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HEREDITARY (?SEX-LINKED) ANEMIA*

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The hereditary nature of numerous hematologic disorders, hemophilia, hereditary hemorrhagic telangiectasia, etc., is well established and generally recognized. Among the inherited blood diseases there are 3 well-defined and not uncommon types of anemia, namely, the anemia associated with familial hemolytic icterus, sickle cell anemia, and Mediterranean anemia. These anemias, in addition to their hereditary factor of etiology, have several features in common. Striking abnormalities in the structure and physiologic behavior of the red blood cells occur in all of them, as well as a tendency toward chronic and sometimes acute episodes of red blood cell hemolysis. Sickle cell anemia, with its underlying erythrocyte abnormality, the sickle cell trait, and Mediterranean anemia are almost exclusively confined by accident or otherwise to certain racial groups. The Mediterranean disease occurs in a mild asymptomatic form as well as in a severe and ordinarily fatal form, Cooley's anemia.[1,8,11,19,23,28,32,34,35,41,42,44] It differs perhaps fundamentally from the other hereditary anemias in that a grave deficiency of hemoglobin in the circulating red blood cells occurs, possibly due to an inborn abnormality of pigment metabolism.[43] The erythrocytes show great variation in size and in shape; nucleated red cells are seen in those with severe anemia; some individuals have predominantly oval or elliptical cells and others have many "target" cells.[2,8,11,37,42] It is important to differentiate here another type of inherited erythrocyte anomaly which is usually of no clinical significance. Elliptocytosis, or ovalocytosis, is known to occur in non-Mediterranean families without either anemia or other evidence of disease being present.[3,14,26,45]

Aside from the 3 well-known varieties of inherited anemia, it is not too uncommon in hematologic practice to encounter patients with an anemia associated with unusual degrees of red blood cell malformation, sometimes with icterus and splenomegaly, whose disease appears to be atypical or of uncertain origin. Many isolated case reports of this type have been published.[5,9,13,15,16,18,24,25,30,31,33,39,42] The hereditary nature of such conditions may easily be overlooked, and confirmatory

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studies are not always possible. In any case it is rare for the family group to be large enough to permit a satisfactory investigation of the hereditary and genetic aspects.

We have had under our observation recently 2 families of non-Mediterranean origin in whom there has recurred through several generations a distinctive type of hypochromic anemia associated with abnormal red blood cells and enlargement of the spleen. Our attention was drawn to the first family by the diagnostic problem presented by a 32 year old soldier who had just been discharged from the army because of a severe anemia of unknown etiology. The character of his blood findings and the fact that his maternal grandfather was known to have had an enlarged spleen all his life with symptoms suggestive of a chronic anemia led us to suspect that a familial type of blood dyscrasia was present. When we discovered that his mother had an enlarged spleen even though her blood values were normal, a complete family investigation appeared desirable. Medical histories, physical examinations and blood studies on all the available relatives, 29 in all, were obtained, largely by field trips to their homes. A severe anemia with splenomegaly was discovered in a brother who had previously been considered perfectly well. In addition to his mother, 4 other female relatives were found to have enlarged spleens or minor blood abnormalities.

In the second family at least 16 males scattered through 5 generations had died of severe anemia during infancy or adolescence. Two brothers afflicted with the anemia were living. One boy's health was precarious and the other required blood transfusions at regular intervals to keep him alive. An investigation similar to that carried out in the first family was accomplished with 18 members being available for study. No unsuspected cases of anemia were found, but 6 of the female relatives, including the afflicted boy's mother and grandmother, were shown to have red blood cell abnormalities and in some cases splenomegaly.

Procedure. To study in some detail the genetic linkage underlying the blood abnormalities in these families, a number of tests and measurements were made in order that the occurrence of traits having an established inheritance pattern might be compared with the hematologic findings. The bloods were typed with respect to the agglutinogens A_1, A_2, B, M, and N. Determination of the taste reaction to phenylthiocarbamide, tests of color vision and eye dominance, and tests of handedness were made. The "secretor factor" was determined on the saliva by means of human A and B serums. The results of these tests and their genetic significance will be discussed separately.

The pedigree charts (Figs. 1 and 3) differ from the conventional diagram by having the children of a single union arranged in a vertical column in the order of their birth rather than horizontally. The sibships are numbered 1 to 18 in Family I, and 1 to 19 in Family II. A specific individual will be referred to by means of the sibship number followed by a number denoting his or her position from top to bottom, corresponding to birth order, within the sibship. Thus, 11–1 of Family I refers to the anemic male first studied, whose grandfather, 2–3, appeared to be the first member of the family to have the disease.

The hematologic findings are given in Tables 1 and 2. Only the data pertaining to the afflicted individuals, their parents, siblings, and those relatives with splenomegaly or minor blood abnormalities are given.

Platelet counts unless otherwise specified were in all cases normal. Prothrombin determinations were done in a few cases, but being normal were deleted along with other various negative findings. It was not possible to get adequate Rh typing at the time.

FAMILY I (Heredity Clinic No. 606). This family was of German, Scotch and English origin, without any of the living members or known ancestors being of Mediterranean stock. The family pedigree is given in Figure 1. Generations I through III originated in Wisconsin and followed farming and laboring occupations. There were no mental abnormalities nor physical stigmata

known in the family. The first member of the family who appeared to be affected with the anemia (2–3) was the grand-father of our first patient. He was always pale, never able at any time during his adult life to do more than light work, and he suffered from numerous fainting spells. A large spleen was said to have been present for many years but no blood examinations were ever made. He lived to be 62 years of age. There were 5 children in his family and 4 of them were living and available for examination. His youngest daughter (6–5) died of an infectious disease when 11 to 12 years old. She was thought not to be anemic nor to have had an enlarged spleen. The case histories of the remaining members of this family and their descendants follow.

R. F. (6–1) was 57 years of age. Except for a period of gastro-intestinal symptoms thought to be due to peptic ulceration he had always been well. A physical examination and a complete blood examination (Table 1) revealed no abnormalities. One of his sons was serving in the army and was not available for examination. The 3 remaining children and 4 grandchildren were healthy, and complete blood and physical examinations revealed no abnormalities.

L. M. F. (6–2) was a 55 year old housewife. She had had no unusual illnesses, no symptoms of anemia, nor jaundice. A

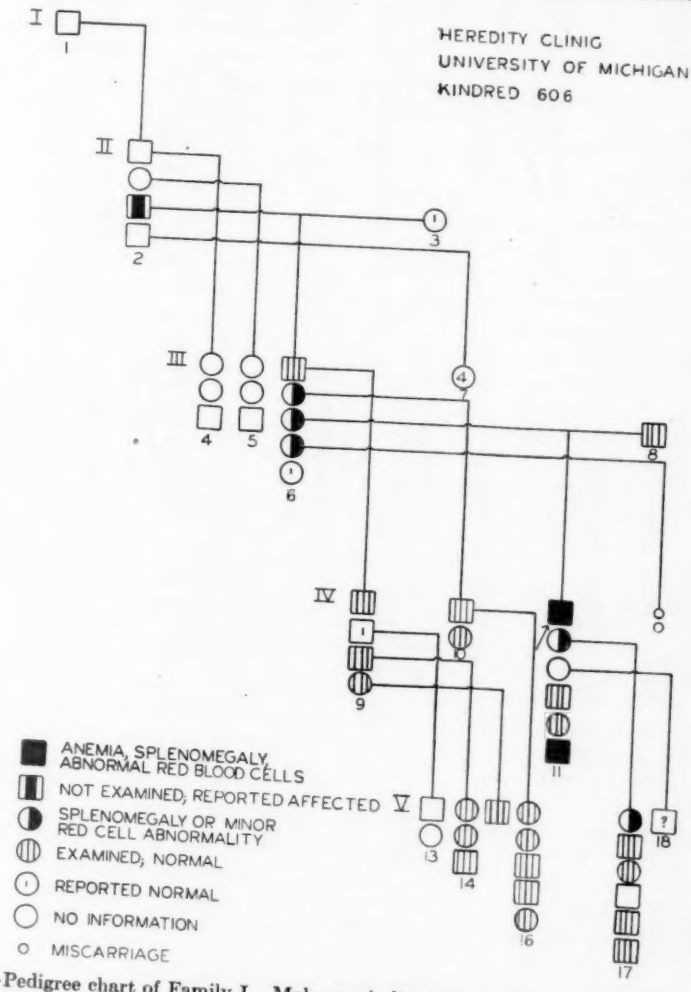

FIG. 1.—Pedigree chart of Family I. Males are indicated by squares, females by circles.

TABLE 1.—SUMMARY OF BLOOD FINDINGS IN FAMILY I

Identity	Age, sex	Hb. (gm. per 100 cc.)	RBC (mill. per c.mm.)	Hemato-crit	M.C.V. (cμ.)	M.C.H. (μμg.)	M.C.H.C. (%)	Morphology of RBC	Reticulo-cyte (%)	Range of hemolysis in hypo-tonic NaCl solutions	Blood type	Other findings
R. F. 6–1	57 M	16.9	5.4	46.5	86	31.3	36.4	Normal	..	...	OMN	
L. M. F. 6–2	55 F	14.2	4.9	40.5	83	29.0	35.0	Anisocytosis +, oval cells 6%				
R. F. P. 6–3	51 F	15.1	4.9	44.5	91	30.8	34.0	Anisocytosis +, oval cells 6%	0.5	0.60–0.45 0.55–0.40*	A_1MN	Splenomegaly
J. P. 8–1	55 M	16.5	5.7	48.0	84	29.0	34.4	Normal	..	0.50–0.35 0.55–0.45*	A_1MN	
B. F. B. 6–4	44 F	12.4	4.2	38.5	92	29.5	32.2	Anisocytosis +, oval cells 5%	0.4	...	A_1BMN	
G. P. 11–1	32 M	9.1	6.4	35.0	55	14.2	26.0	Anisocytosis ++++, poikilocytosis ++++, target cells 6%	3.1	0.55–0.15 0.55–0.35*	A_1M	Splenomegaly, hepatomegaly
L. P. C. 11–2	30 F	15.4	5.0	45.0	90	30.8	34.2	Anisocytosis +	2.0	0.55–0.40 0.55–0.35*	A_1M	
H. P. 11–5	23 F	15.0	4.6	42.3	92	32.6	35.5	Normal	..	0.50–0.40 0.55–0.40*	A_1N	
R. P. 11–6	15 M	10.4	5.5	35.7	65	18.9	29.1	Anisocytosis +++, poikilocytosis +++, target cells 0.5%	1.0	0.50–0.25 0.55–0.45*	A_1MN	Splenomegaly
L. C. 17–1	10 F	13.1	4.9	..	..	..	..	Anisocytosis +	0.5	...	A_1MN	Splenomegaly
R. M. 18–1	3½ M	15.5	5.4	..	..	..	..	Anisocytosis +, poikilocytosis +, spherocytes 10%	..	...	OMN	Palpable liver and spleen

* Normal control.

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physical examination showed no abnormalities. The blood examination showed that there was no anemia but in the stained films the red blood cells varied beyond normal in size and 6% were oval in shape. Her 2 children and 5 grandchildren were likewise examined and found to be normal.

B. F. B. (6–4). This 44 year old married woman had had good general health. When 31 years old she had a prolonged febrile illness thought to be due to a brucella infection. Two miscarriages in mid-pregnancy occurred some years later. When 41 years of age symptoms of a severe anemia led to the discovery of a hemoglobin level 43% of normal. This was attributed to hypermenorrhea associated with uterine fibroids, and the blood counts improved with treatment. Physical examination showed no abnormalities and the peripheral blood values were within range of normal (Table 1). The red blood cells varied somewhat beyond the usual in size, 5% of them were oval in shape, but all were well and uniformly filled with hemoglobin.

R. F. P. (6–3). This 51 year old woman, the mother of 2 anemic sons, had always had good general health. She had never been anemic or jaundiced and splenomegaly had never been previously discovered. A physical examination showed that she was well developed and well nourished. No physical abnormality was found other than an enlarged, firm, movable spleen, the tip of which descended 3 to 4 cm. below the costal margin with inspiration. The peripheral blood values and red cell fragility tests were normal (Table 1). The red blood cells varied slightly beyond normal in size and a small percentage of them were oval shaped but well and uniformly filled with hemoglobin. Her husband (J. P., 8–1) had had no illnesses other than asthma which was associated with exposure to dusts. There was no consanguinity. A physical examination revealed no relevant abnormalities and his blood values and red cell fragility tests were normal.

G. P., No. 542654 (11–1). This 32 year old son of R. F. P. (6–3) was admitted to the Simpson Memorial Institute on Feb. 28, 1944, shortly after being discharged from the United States Army. His general health had been perfectly good until 2½ years earlier when an acute febrile illness led to his admission to a local hospital. An enlarged spleen was discovered and it was thought that he had malaria. The fever subsided after a few days and the spleen became smaller. He soon felt well again and returned to his work in an automobile factory.

In June 1943, he was inducted into the Army. He was able to perform all the training exercises except that he was unable to march double time for more than 1 or 2 blocks. In the latter part of November 1943, he developed a mild upper respiratory infection and while on a hike became weak and short of breath. At the station hospital that evening a temperature of 103° F. was found. The fever continued for several days. He was told that he was jaundiced, that his liver and spleen were enlarged, and that his hemoglobin was 40% of normal. Coincident with the administration of iron he gradually improved and was discharged from service 10 weeks later. He consulted us because his final discharge diagnosis appeared to be uncertain and the outlook was worrisome.

Physical examination on admission to the hospital showed the patient to be well developed and well nourished. His complexion was yellowish but there was no visible icterus. The blood pressure was normal. Examination of the head and neck revealed no abnormalities. The heart and lungs were normal. The liver was enlarged, the lower edge extending across the abdomen 10 cm. below the ensiform process to a point 5 cm. below the lateral rib margins on the right side. The spleen was enlarged to fill the left upper quadrant of the abdomen, the tip being palpable 5 cm. below the costal margin at respiratory rest. The remainder of the physical examination showed nothing abnormal.

A urinalysis, Kahn test, and a stool examination were negative. The serum bilirubin was 0.83 mg. per 100 cc. and the urine urobilinogen excretion was slightly increased. Roentgen examination of the upper gastro-intestinal tract showed no intrinsic abnormality but confirmed the finding of an enlarged liver and spleen. The gall bladder was not made visible. Roentgenograms of the chest, hands, wrists, and skull were not abnormal. The cephalin flocculation test and bromsulphthalein test showed no evidence of impaired liver function. Examination of the peripheral blood

* Normal control.

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disclosed a severe hypochromic microcytic anemia (Table 1). The red blood cells showed extreme variation in size, in shape and in hemoglobin content (Fig. 2, *A*). In fresh sealed preparation the bizarre red cell forms were equally conspicuous and after 48 and 72 hours there was no change in morphology. No nucleated red blood cells were present. The erythrocytes showed some increased resistance to hemolysis in hypotonic sodium chloride solutions. The white blood cell and differential counts were normal, and there was no shift toward immaturity in the myeloid cells.

The bone marrow obtained by sternal puncture was less cellular than normal. The predominant nucleated cells were relatively mature granulocytes with a small percentage of myelocytes. Typical hemohistiocytes were present. Normoblasts were fairly numerous, erythroblasts less common, and megaloblasts rare and atypical. The myeloid-erythroid ratio was about 5 to 1. A splenic puncture was done and the spread films contained clumps of mononuclear phagocytic cells. There was no evidence of splenic hematopoiesis.

The patient was afebrile and entirely comfortable during his hospital stay and after discharge he was able to resume heavy labor. There was no change in the blood values after several weeks of iron therapy. Nine months later his general condition remained unchanged and his blood values were unaltered.

L. P. C. (11–2), the 30 year old sister of G. P. (11–1) and the mother of 6 children, had enjoyed good health except for biliary colic and jaundice due to cholelithiasis for which a cholecystectomy had been done. Physical examination showed pronounced obesity. The liver was palpable 2 to 3 cm. below the right costal margin but the spleen could not be felt. The peripheral blood values were within the average range for healthy individuals. The red blood cells varied beyond normal in size and a few were oval in shape and somewhat deficient in hemoglobin content.

Five of her 6 children were living, in good health, and available for examination. Her fourth child, a boy, had died at 9½ months, of congenital heart disease. L. C. (17–1), the oldest girl, enjoyed robust health and had never been anemic, jaundiced, nor had chills or fever. Physical examination on 2 occasions several months apart showed as the only abnormality an enlarged spleen, the broad, rounded tip of which descended 2 to 3 cm. below the costal margin with inspiration. Her blood values (Table 1) were not abnormal. A few of the RBC were oval in shape, but well and uniformly filled with hemoglobin. In fresh, moist preparations there was no sickling after 48 hours. Similar physical and blood examinations in the 4 younger children in this family showed no abnormalities.

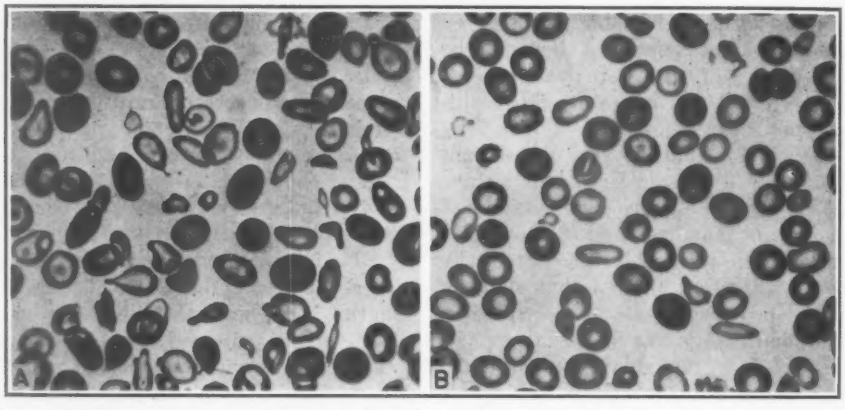

FIG. 2.—Stained blood films of the anemic males in Family I. *A*, G. P., 11–1; *B*, R. P., 11–6.

E. P. (11–3) had always been considered perfectly healthy but died at the age of 23 years of a postpartum pulmonary embolus. Her 3½ year old son (18–1) had been unusually susceptible to childhood diseases and during infancy he had had rickets. He

had had no known anemia and had never been jaundiced. Physical examination on 2 occasions, several months apart, showed both the liver and spleen to be palpable 1 to 2 cm. below their respective costal margins. The red blood cell count and hemoglobin values were normal. The red blood cells were mostly round but they varied beyond normal in size and in shape, and about 10% of the cells were spherocytes.

H. P. (11–4) was considered healthy in all respects and was in active service in the Army. Blood counts forwarded from the Far East by Major Charles A. Armbrust were normal.

H. P. (11–5) was a 23 year old factory

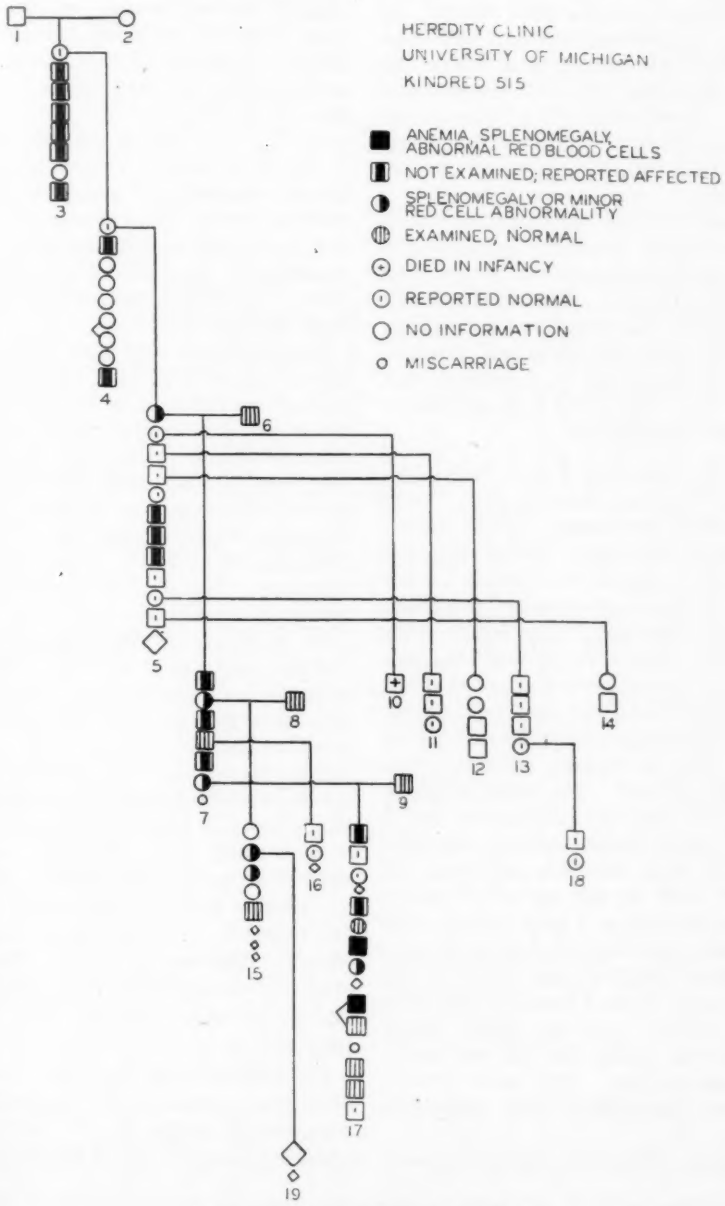

FIG. 3.—Pedigree chart of Family II.

worker. She had been jaundiced for a few weeks 4 years previously. On physical examination a tender liver edge was palpable just below the costal margin, but the spleen was not palpable. Blood counts and fragility tests were normal and the red blood cells were normal in morphology.

R. P. (11–6), the youngest brother of G. P. (11–1), was a 15 year old schoolboy who had always enjoyed robust health. He was fond of strenuous sports and had never been jaundiced nor had unusual febrile episodes. A complete physical examination showed no abnormality other than an enlarged spleen the lower border of which was palpable 2 to 3 cm. or more below the left costal margin.

Examination of the peripheral blood on different occasions showed a hypochromic microcytic anemia slightly less severe than of his brother (Table 1). The red blood cells varied greatly in size, shape and hemoglobin content (Fig. 2, *B*), and there was increased resistance to hemolysis in hypotonic salt solutions. The white blood cells and differential counts were normal.

FAMILY II (Heredity Clinic No. 515). This family originated from English, Dutch and Swiss stock which was without known Mediterranean admixture. Some members of the family migrated to Canada in the 1880's and the last 4 generations have made their home in Michigan. The family pedigree is given in Figure 3. Typical examples of the familial anemia were first noted about 1810 in Holland when in 1 family (3) 6 male children died in infancy of pallor and bloodlessness.* The 2 female children were healthy and survived. The older daughter in later years had, in addition to her 7 apparently healthy female children, 2 anemic sons. One of them was pale and sickly all his life but lived to the age of 17 years. In the next generation 3 male infants died of the anemia when between 2 and 6 months old. The oldest child in this sibship (5–1), the grandmother of the 2 living anemic boys (17–7 and 17–10), was the oldest living individual in the family and she was available for examination. Her case history, those of her descendants and collaterals follow.

L. G. (5–1). This 65 year old grandmother had always had good general health without unusual illnesses. She had never been jaundiced and had had no chills, fever or known anemia. Physical examination on Nov. 6, 1944, showed pronounced obesity. There was no icterus and her liver and spleen could not be palpated. The peripheral blood counts and values were normal (Table 2). The red blood cells varied slightly beyond normal in size, but they were well and uniformly filled with hemoglobin. Four % of them were pale cells, oval in shape, similar to those in her daughter's blood (Fig. 4, *A*).

A. P. (6–1), the 66 year old husband of L. G. (5–1), was of French origin and had always enjoyed good general health. There were no known blood diseases in his family and there was no consanguinity. Physical examination disclosed no abnormalities and there was nothing unusual in the hematologic findings (Table 2).

Seven children were born to these parents. The oldest child (7–1), a boy, was pale and weak from the time of his birth. He was never well but lived to be 13 years of age when he died of "starvation of the blood." The third and fifth children were males who died of the anemia at about 4 months and 2 months of age, respectively. The seventh child died at birth, the cause of death being unknown. The 3 remaining children were living and examined.

M. P. M. (7–2). This 45 year old woman had had fairly good general health. In her teens she had several episodes of fever and later developed an acute arthritis of several months duration. After bearing several viable children she had 3 miscarriages and developed some gynecologic symptoms which finally led to a laparotomy and the removal of an ovarian cyst. Physical examination showed apparent good health. There was no jaundice and her liver and spleen were not palpable. The peripheral blood values were not definitely abnormal. The erythrocytes varied slightly beyond normal in size and 6% of them were the pale, thin, oval cells.

Her husband and 4 of their 5 living children were available for examination. All were normal except for 2 of the daughters who had the same minor blood abnormality

* We are indebted to Dr. T. B. Cooley for information regarding sibships 1, 2 and 3. The children in sibship 17 were under his care for a number of years.

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TABLE 2.—SUMMARY OF BLOOD FINDINGS IN FAMILY II

Identity	Age, sex	Hb. (gm. per 100 cc.)	RBC (mill. per c.mm.)	Hematocrit	M.C.V. (cμ.)	M.C.H. (μμg.)	M.C.H.C. (%)	Morphology of RBC	Reticulocyte (%)	Range of hemolysis in hypotonic NaCl solutions	Blood type	Other findings
L. G. 5–1	65 F	14.6	4.7	42.0	89	31.0	34.8	Anisocytosis +, oval cells 4%	1.0	...	A_1MN	
A. P. 6–1	66 M	15.4	4.9	47.0	96	31.4	32.8	Normal	..	...	OMN	
M. P. M. 7–2	44 F	13.0	4.0	38.0	95	32.5	34.2	Anisocytosis +, pale, oval cells 6%	2.0	...	OMN	
V. M. A. 15–2	21 F	13.6	4.6	43.0	94	29.5	31.6	Anisocytosis +, pale, oval cells 10%	1.1	...	BMN	
F. M. S. 15–3	20 F	12.8	4.4	37.0	84	29.1	34.6	Anisocytosis ++, pale, oval cells 20%	2.0	...	A_1MN	Spleen palpable
L. E. P. 7–4	44 M	14.9	5.2	44.5	85	28.6	33.4	Normal	..	...	A_2MN	
R. P. C. 7–6	39 F	14.8	4.5	42.5	95	32.8	34.8	Anisocytosis +, pale, oval cells 3%	1.2	0.55–0.45 0.55–0.40*	ON	Splenomegaly
J. C. 9–1	43 M	14.9	5.4	46.0	85	27.6	32.4	Normal	..	0.55–0.35 0.55–0.40*	BMN	
D. J. C. 17–6	14 F	13.0	4.8	40.0	84	27.0	32.4	Normal	..	...	BN	
R. C. 17–7	13 M	7.0	5.5	27.0	49	12.7	25.9	Anisocytosis ++++, poikilocytosis +++	1.6	0.55–0.15 0.50–0.40*	OMN	Splenomegaly, hepatomegaly
M. M. C. 17–8	12 F	13.1	4.3	38.0	88	30.2	34.5	Anisocytosis ++, pale, oval cells 10%	1.0	...	BN	Splenomegaly
J. C. 17–10	9 M	5.6	2.8	20.0	71	20.0	28.0	Nucleated RBC, anisocytosis ++++, poikilocytosis +++	5.0	0.50–0.20 0.50–0.40*	BMN	Past splenectomy
G. C. 17–11	9 M	13.2	5.5	41.0	75	24.0	32.2	Normal	..	0.50–0.40 0.55–0.40*	OMN	Palpable spleen
E. C. 17–13	6 M	13.6	5.2	40.0	77	26.1	34.0	Normal	..	...	BMN	
M. C. 17–14	4 M	13.1	5.2	39.0	75	25.1	33.6	Normal	..	...	ON	

* Normal control.

as their mother, and in 1 of them the spleen was palpable. Their case histories follow.

V. M. A. (15–2), the 21 year old married daughter of M. P. M. (7–2), had an acute type of arthritis at the age of 4 years, but afterward she was well. Her first child died 5 hours after delivery by Cæsarean section and her second pregnancy ended in a spontaneous miscarriage at 3 months gestation. Physical examination showed no abnormalities and neither the liver nor the spleen was palpable. The peripheral blood values were normal. Many of the erythrocytes varied beyond normal in size, in shape, and in hemoglobin content and 10% of the cells were the small, pale, oval type.

F. M. S. (15–3). This 20 year old married sister of V. M. A. (15–2) had enjoyed good general health in spite of an unusual number of childhood diseases, an appendectomy at 10 years of age, and an operation for "suspending" the uterus at the age of 19 years. Her one pregnancy had terminated a few weeks previously in a spontaneous miscarriage after $4\frac{1}{2}$ months gestation. Physical examination showed good general development. Her liver was not palpable. A slender spleen was palpable well below the costal margin deep in the left upper quadrant of the abdomen, but it did not seem to be definitely larger than normal.

The peripheral blood values were not unusual. The stained red blood cells, however, were definitely abnormal in morphology, showing excessive variability in size, in shape, and in hemoglobin content with 20% of them being the small, oval and pale cells (Fig. 4, *B*). A rare cell contained several tiny, darkly stained inclusions.

L. E. P. (7–4). This 44 year old male

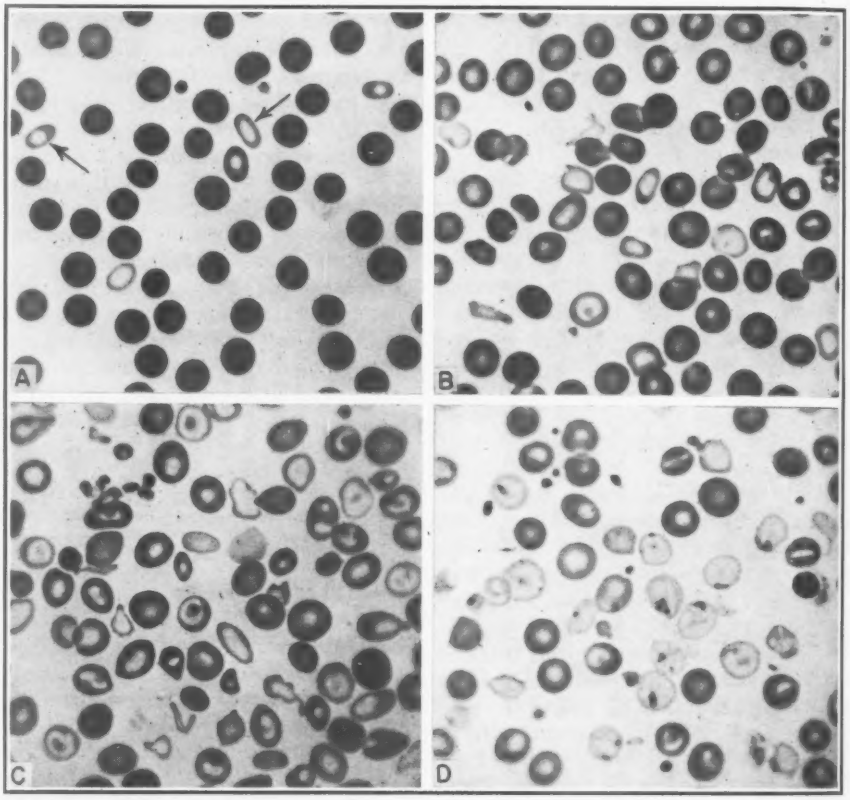

FIG. 4.—Stained blood films of members of Family II. *A*, R. P. C., 7–6. Five of the pale, oval cells are seen in the field and 2 of them are indicated by arrows. *B*, F. M. S., 15–3; *C*, R. C., 17–7; and *D*, J. C., 17–10.

had always been well. He had never been jaundiced, nor had chills or fever. Physical examination showed no abnormalities other than an inguinal hernia. The liver and spleen were not palpable. The blood values and the erythrocyte morphology were normal.

R. P. C. (7–6) was the 39 year old mother of the 2 living anemic boys (17–7 and 17–10), and she had never been seriously ill. At the age of 15 years she had hypermenorrhea and was thought to be anemic at that time. She had never been jaundiced nor had she chills or fever. Following her fifteenth pregnancy relaxation of the pelvic floor was corrected by a hysterectomy and a plastic operation. Physical examination showed no abnormalities other than an enlarged spleen which filled much of the left upper quadrant of the abdomen, the broad tip of it descending 2 to 3 cm. or more below the costal margin at the beginning of inspiration. The peripheral blood values were normal. The red blood cells varied slightly in size and in hemoglobin content; 3% of them were small, pale, oval cells (Fig. 4, *A*).

J. C. (9–1), the 43 year old husband of R. P. C., had had no serious illness and he was in good general health. There was no consanguinity. Physical examination and a complete blood examination revealed no abnormalities.

J. C. C. (17–1). At birth this boy appeared to be a normal infant and weighed 6¾ pounds. After a few days he gradually became pale, weak, ate poorly and lost weight. Coughing and vomiting developed and he died when 3 months and 7 days old.

L. W. C. (17–2). This boy was always well and at the age of 18 years began service in the U. S. Navy. He was not available for examination.

R. M. C. (17–3). Until the age of 7 years this girl was healthy but she then contracted rheumatic fever. She died of cardiac failure 2 years later.

J. C. (17–5). This male infant had the exact symptoms and clinical course as 17–1 and died of the anemia when 3 months and 8 days old.

D. J. C. (17–6) was a 14 year old schoolgirl who had always enjoyed robust health. A physical examination and a complete blood examination showed no abnormalities.

R. C., No. 543696 (17–7). This 13 year old schoolboy was first seen at the Simpson Memorial Institute on March 13, 1944. His general health had never been more than fairly good. At birth he appeared to be normal and weighed 6 pounds. After a few weeks, however, like the 2 previous male infants, he began to eat poorly and became extremely pale. At the age of 3 months the family physician discovered that his hemoglobin was 10% of normal and did not expect him to live. A variety of hormone preparations were administered and he began to improve slowly. After the age of 1 year he had no serious symptoms but he was never strong or vigorous. Common illnesses affected him severely and convalescence was often prolonged. When 11 years old he began to work after school hours and he soon became weak and generally ill. One blood transfusion was required at that time before he began to regain his usual degree of health.

Physical examination showed him to be fairly well developed and somewhat underweight. His face was pale and pudgy but there was no icterus. His heart was at the upper limits of normal in size. The spleen was enlarged to fill the left upper quadrant of the abdomen, with the inferior margin being palpable 4 cm. below the left costal margin. The liver edge was felt 2 to 3 cm. below the margin of the ribs on the right side. No other physical abnormalities were found.

Roentgen examination of the skull, chest, spine and hands showed no bony abnormality.

Examination of the peripheral blood (Table 2) showed the presence of a severe hypochromic microcytic anemia. Nearly half of the red blood cells were oval and all of them varied to extreme degree in size, in shape, and in hemoglobin content (Fig. 4, *C*). There was no change in erythrocyte morphology in fresh sealed preparations after 48 hours. Target cells numbered 0.3% and reticulocytes 1.6%. A rare cell contained several tiny darkly stained inclusions. A hypotonic saline fragility test showed increased resistance of the erythrocytes to hemolysis. The white blood cell and differential counts were normal.

He was seen at intervals for several months during which time his general condition and his blood status remained unchanged.

M. M. C. (17–8) was a 12 year old school-

girl who had had only the common childhood diseases and her general health was good. Physical examination showed no abnormalities except an easily palpable spleen, the tip of which lay 1 cm. or so below the left costal margin at the beginning of inspiration. The peripheral blood values were not abnormal. In the stained blood films the red blood cells varied beyond normal in size and in hemoglobin content. Ten % of the erythrocytes were small, oval and extremely pale.

J. C., No. 543350 (17–10). This 9 year old boy was admitted to the Simpson Memorial Institute on April 3, 1944. He was one of dissimilar twins and he had never been well. At birth he appeared to be a healthy infant of about average weight. After a few weeks he became pale, sickly, and ate poorly as had the other afflicted male children in his family. With the onset of these symptoms his diet was supplemented with cod liver oil, cooked and powdered liver, and tomato juice. After a few months he gradually improved and for 3 or 4 years he was reasonably healthy. When 5 years of age he suffered a minor cut with trauma to his knee and shortly afterward he became very pale and generally ill. He was taken to his local hospital where an enlarged spleen and a severe anemia were found. The blood values did not improve with the prolonged administration of many liver, iron and vitamin preparations, and blood transfusions at regular intervals became necessary to keep him alive. Nearly 50 transfusions were given during the next 4 years. One year before admission his spleen was removed at the Children's Hospital in Detroit. This resulted in no improvement and, if anything, his blood values dropped faster than before the operation. He continued to tire easily and vigorous activity could not be tolerated. Jaundice, chills and fever had never occurred.

Physical examination at the time of admission showed him to be pale and underdeveloped but well nourished. His face appeared pudgy but not mongoloid. There was no icterus. His heart was slightly enlarged and a moderately loud systolic murmur was audible at the apex. There was a well-healed splenectomy scar in the left upper abdominal wall. The liver edge could not be palpated and the area of hepatic dullness was not increased. The remainder of the physical examination disclosed no abnormalities.

Urinalysis and a stool examination were normal. The serum bilirubin was 0.5 mg. per 100 cc. and the urine urobilinogen excretion was not increased. The cephalin flocculation test of hepatic function was 2+ positive. Roentgen films of the chest confirmed the slight cardiac enlargement and additional films of the skull, spine and hands showed no skeletal abnormality.

The peripheral blood values (Table 2) were those present 7 weeks after he had been transfused with 785 cc. of red blood cells. In the stained films, about 40% of the cells appeared to be donor's cells. The patient's erythrocytes were extremely thin and many contained so little hemoglobin as to be nearly invisible (Fig. 4, *D*). There was extreme variability in size and shape, and the majority contained tiny Howell-Jolly bodies in addition to inclusions similar to those described by Pappenheimer, Thompson, Parker and Smith.[31] Six % were target cells and 5% were reticulocytes. There were 65 nucleated erythrocytes for every 100 white blood cells. The number of platelets was greatly increased. The white blood cell count, when corrected for the number of nucleated red cells present, was normal. The appearance of the stained white cells and the differential count were normal, without myeloid immaturity being present. After a series of blood transfusions had been given nucleated red blood cells became rare. It was said that the red blood cell morphology before his splenectomy was identical with that of his brother, R. C. (17–7).[10]

G. C. (17–11) was the 9 year old dissimilar twin of J. C. (17–10). He had always been small in stature but in excellent health. He had had no unusual illnesses or symptoms. Physical examination showed no definite abnormalities although the tip of the spleen was palpable 1 cm. below the left costal margin at the end of deep inspiration. The blood values and cellular morphology were not abnormal.

E. C. (17–13) and M. C. (17–14) were healthy boys, 6 and 4 years old, respectively. Physical examinations and blood examinations showed no abnormalities. J. C. (17–15), the youngest child, was a healthy infant who died at the age of 1 year of pneumonia.

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During the course of this study we have encountered at least 4 additional patients, unrelated to the 2 families just described, who had chronic types of refractory anemia resembling those of known hereditary origin. They presented much the same type of clinical problem as the white woman of non-Mediterranean origin reported by Valentine and Neel,[42] who had a chronic hypochromic anemia refractory to iron therapy that showed many of the characteristics of thalassemia minor. The blood of both of her parents was normal and the hereditary nature of the blood disorder could not be proved. One of our patients (D. C., No. 543866) was a 22 year old white housewife whose ancestors were of northern European stock. A severe anemia was discovered during her first pregnancy and this was again found to be present after a febrile illness. No frank symptoms of anemia were ever present. During the 6 months prior to our examination her red blood cell count ranged between 2,800,000 and 3,410,000 per c.mm., and the hemoglobin between 36 and 67% of normal, despite 9 blood transfusions and many injections of liver extract.

Physical examination showed that there was no icterus and neither the liver nor the spleen was enlarged. Roentgenograms of the skeleton showed no abnormality. Examination of the peripheral blood 4 days after the last blood transfusion (Table 3) showed that a normocytic anemia was still present and that her erythrocytes varied far beyond normal in size and in hemoglobin content. There was no increase in reticulocytes. The white blood cell count was 4300 per c.mm., and of these 2% were myelocytes, 2% metamyelocytes, 0.5% hemohistocytes. The sternal marrow was less cellular than normal but it contained abundant normoblasts, fewer erythroblasts, and not infrequent megaloblasts. The erythroid cells outnumbered the myeloid cells 4 to 1. The blood transfusions were discontinued and she remained in good health during the following year. A second blood examination showed slightly improved blood values and at this time there was no immaturity of the myeloid cells. The blood of several relatives was examined and her mother was found to have a hypochromic microcytic anemia (Table 3) with disproportionately deformed red blood cells.

A second patient (M. E., No. 340785), a woman of middle European ancestry, was 26 years of age when she was first seen for consultation regarding a chronic anemia. She had been free of infection, had had no unusual blood loss and had never been icteric. There were no physical abnormalities other than that her spleen was palpable just below the costal margin. The blood bilirubin was 0.59 mg. per 100 cc. A gastric analysis showed average amounts of free hydrochloric acid. A hypochromic, microcytic anemia was present with an unusual degree of red blood cell distortion (Table 3). There was no improvement in the blood status after many courses of iron therapy, liver and vitamin preparations, etc. The blood values fluctuated but little over an observation period of 10 years. No members of her family were available for investigation.

A third patient (L. U., No. 266609) was a male of non-Mediterranean origin, 36 years of age when he was first seen in 1931, a few weeks after chronic fatigue and a yellowish complexion led to the discovery of a severe anemia with conspicuous red blood cell malformation (Table 3). At that time the only physical abnormality was slight enlargement of the spleen. There was no evidence of blood loss. After 3 months treatment with iron and other medications the red blood cell count rose to 4,400,000 while the hemoglobin remained between 50 and 64% (Sahli). There was little change in erythrocyte morphology. He enjoyed fairly good general health during the next 11 years but following a febrile illness early in 1943 a severe anemia recurred (Table 3). Physical examination showed that there was no jaundice. The spleen had enlarged slightly more to become palpable 3 cm. below the costal margin at respiratory rest. The blood bilirubin was 0.5 mg. per 100 cc. There was no improvement with several types of anti-anemic therapy, oral and intravenous iron, liver extract injections, etc., and repeated series of blood transfusions became necessary. Five months later an exploratory laparotomy was advised since a number of stools had given positive guaiac tests. At operation the abdominal organs appeared grossly normal and no source of intestinal bleeding was found. It was decided to remove the spleen and a biopsy of the liver was taken.

The blood values gradually improved for a time but the red blood cells became even more bizarre in size and shape with about 40% of them containing Howell-Jolly bodies or minute inclusions (Table 3). His clinical condition did not improve, however, and he died in July 1944, 1 year after the splenectomy. Pathologic examination of the spleen, the liver tissue removed by biopsy, and the organs removed at autopsy showed extensive deposit of golden brown pigment which with special staining was shown to contain abundant iron. The pathologic findings were said to resemble closely those of hemochromatosis as do those in erythroblastic anemia.[43] The blood findings throughout life were compatible with an hereditary type of anemia, but no relatives were examined. The conspicuous alteration in the red blood cell morphology following splenectomy may be of diagnostic significance since these changes have been largely confined to individuals with some variety of hereditary anemia.[1,2,5,29,31,36,39]

A fourth patient (A. E. S., No. 276728) was a 64 year old laborer born in Michigan. His family was of British extraction without known Mediterranean ancestry. He was treated at the University Hospital in 1931 for carcinoma of the lip and from 1941 to 1945 for recurrent peptic ulceration with hemorrhage. During the later admissions abnormally shaped red blood cells were observed, but the anemia associated with the gastro-intestinal bleeding always responded to iron therapy. The erythrocyte deformity persisted, however, with the return to normal blood values (Table 3). There was no hepatomegaly or splenomegaly and he was never icteric. There was no knowledge of blood abnormalities in other members of his family but an investigation of them has not yet been carried out.

TABLE 3.—BLOOD FINDINGS IN CASES OF ATYPICAL ANEMIA RESEMBLING THOSE OF HEREDITARY ORIGIN

Patient	Age, sex	Hb. (gm. per 100 cc.)	RBC (mill. per c.mm.)	Hemato-crit	M.C.V. (cμ.)	Reticulo-cyte (%)	Morphology of RBC
D. C.,		(3/16/44)					
No. 543866	22 F	9.9	3.6	31.5	87	1	Anisocytosis ++, poikilocytosis +, oval cells 15%, rare nucleated RBC
		(2/21/45)					
		11.2	3.8	35.5	93	..	Unchanged
J. E. (mother of D. C.)	52 F	8.8	4.7	32.0	68	1	Anisocytosis ++, poikilocytosis +, oval cells 15%
M. E.,	26	7.8	3.6	29.0	54	2	Anisocytosis ++,
No. 340785	F	to	to	to	to		poikilocytosis ++, target cells, pencil, fragmented and stippled cells present
		10.7	5.0	36.5	68		
L. U.,		(6/9/31)					
No. 236609	36 M	7.5	2.8	...	...	No incr.	Poikilocytosis ++++, many pencil cells
		(2/21/43)					
		3.0	1.8	11.0	62	2	Anisocytosis ++, poikilocytosis +++, spindle and pencil cells
		(12/2/43)					
		8.8	4.9	30.5	62	2.5	Anisocytosis ++++, poikilocytosis ++++, fragmented and pencil cells, target cells 8%, cells with Howell-Jolly bodies 40%
A. S.,	64	13.1	5.7	45.0	79	..	Anisocytosis +++,
No. 276728	M						poikilocytosis ++++, spindle, racquet and pencil cells abundant

Discussion. A hypochromic microcytic anemia, with irregularly shaped red blood cells varying greatly in hemoglobin content, splenomegaly and sometimes hepatomegaly has been observed to recur in 2 families through several generations. A noteworthy feature of the anemia in these families is its restriction to those of the male sex. In one family the disease becomes manifest early in life and usually terminates fatally at an age of 4 to 6 months. Only a few of the afflicted males live to puberty. In the other family symptoms of anemia did not appear in 1 case until there was apparently an episode of acute erythrocyte hemolysis at the age of 29 years. A younger brother who was afflicted appeared well and healthy at the age of 15 years, and the degree of his anemia, erythrocyte abnormality, and splenomegaly was less at that age. The physical and blood findings in the case of their 3½ year old nephew appeared to be significantly abnormal and it is possible that in later life he will develop a similar anemia. Only through repeated observations through the years, however, will the eventual prognosis in the latter family be established and the appearance of the disorder at different periods of life be determined.

The anemia appears to be transmitted from generation to generation by 1 parent only and follows a pattern compatible with sex-linked inheritance in which the character is recessive, or incompletely recessive, in females. Anemia was not found in any of the females, even in those who were known to have transmitted the disease to their sons, but several of them could be recognized as carriers of the disease trait by the presence of an enlarged spleen or by certain erythrocyte abnormalities. In Family I the mother, R. F. P. (6–3), of the 2 anemic males was certainly a carrier of the trait and she had a definitely enlarged spleen. Her peripheral blood values were normal and her red blood cells showed excessive variation in size. Four other females in the family (6–2, 6–4, 11–2, and 17–1) were throught probably to be carriers of the anemic trait because of similar minor erythrocyte abnormalities with 1 of the women having in addition a demonstrable splenomegaly. Roentgen examination of the 3 women without palpable spleens, 1 of whom was very obese, might have disclosed enlargement of the spleen but these procedures were not feasible.

In Family II, both L. G. (5–1) and R. P. C. (7–6) transmitted the anemia to their children. Their carrier state could be established more easily and with more certainty than in the other family by a greater variation in size and in hemoglobin content of their erythrocytes and by the presence among them of small, pale, oval cells. R. P. C. (7–6) had in addition a definitely enlarged spleen which obesity might have obscured in L. G. (5–1). Four other females in this family (7–2, 15–2, 15–3 and 17–8) had similar erythrocyte abnormalities and were thought also to be carriers of the anemic trait. None of them were anemic and in 2 cases the spleen was palpable. The number of small, pale, oval red blood cells in their blood ranged from 6 to 20%. These erythrocyte abnormalities were more conspicuous in the younger women and most pronounced in F. M. S. (15–3) who had recently had a miscarriage after 4½ months gestation. The effect of pregnancy, infection, and blood loss in these individuals was not studied further. The possible relation of the carrier state to the frequent miscarriages is difficult to evaluate, particularly since the sex of the fetuses was not recorded.

R. F. P. (6–3) in Family I and both L. G. (5–1) and R. P. C. (7–6) of Family II had normal sons as well as anemic sons, thus proving themselves to be heterozygous for the gene responsible for the anemia. M. P. M. (7–2) in Family II had a normal daughter, 2 carrier daughters, and 1 normal son and likewise appears to be heterozygous. The other females showing evidence of being carriers of the abnormal gene may be presumed to be heterozygous, also.

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Sex-linkage, a relatively common type of human inheritance, in our opinion, appears to be the most likely genetic mechanism operating in the inheritance of the anemia in these families. Another less frequent mode of heredity is possible, however, that of an autosomal dominant character reaching full expression in males and being incompletely recessive in females. Sex-linked inheritance can be distinguished from autosomal sex-limited or sex-influenced inheritance only by the study of descendants of affected males. Unfortunately only 1 such male, 2–3 in Family I, had offspring. His 1 son was normal as would necessarily be the case if the disease were sex-linked; but if it were autosomal and dominant the son would have had only an even chance of being normal. All female children of such individuals in sex-linked inheritance would be carriers of the trait, as indeed his 3 daughters appeared to be. This could occur by chance, of course, if the inheritance were autosomal and dominant. To determine whether the anemia could reach its full expression in females, homozygous individuals from matings between female carriers and affected males would be necessary. Such matings did not occur in either family and, therefore, there is no information on this point. Study of the results of the various heredity test factors, color vision, blood types, secretor factor, etc., were consistent with the stated paternity relationships but failed to indicate any evidence of genetic linkage between them and the anemia being studied. Final proof of the genetic linkage of the hereditary anemia in these families must await the study of future generations.

The 2 families described here are the first ones reported in which a sex-influenced or sex-linked anemia has been found. In the other hereditary anemias the mode of inheritance is different. In sickle cell anemia and in familial hemolytic icterus males and females are affected alike and either sex may transmit the disease to their children.[12,17,21,38] Recent studies of families with Mediterranean anemia indicate that this anemia occurs roughly in 2 grades of severity, in a mild usually asymptomatic form "thalassemia minor," and in a severe usually fatal form, "thalassemia major" or Cooley's anemia. When the parents of children with thalassemia major are studied, significant blood abnormalities have been present in nearly every case in both parents.[23,28,34,35,42,44] It is thought that the carrier state, thalassemia minor, is due to heterozygosity for a factor which when homozygous results in the severe anemia, thalassemia major.[42] This is of interest in comparison with the inheritance of elliptocytosis in non-Mediterranean races. Elliptic red blood cells are found with equal frequency in males and in females and the anomaly is transmitted by both sexes as a simple dominant characteristic.[3,7,14,22,26,36,45] The majority of individuals with elliptic erythrocytes are not anemic but healthy, long lived, and not unusually subject to disease. One instance of a mating between 2 individuals both having elliptic red cells has been recorded.[45] One female child of these parents developed a hypochromic anemia with splenomegaly, a positive indirect van den Bergh reaction, greatly increased red cell fragility, reticulocytosis and spherocytosis. A history of having had hemolytic crises with icterus was obtained. This severe hemolytic tendency may indicate the results of homozygosity for the elliptic cell trait. Other cases of splenomegaly and jaundice in elliptic cell bearers have been reported,[45] and Leitner[27] has recently studied another family in which this occurs.

The hematologic features of the hereditary, sex-linked anemia are more comparable to those of severe Mediterranean anemia than to any other recognized entity. The degree of hemoglobin deficiency, the microcytosis and conspicuous red blood cell malformation is similar in both conditions. Erythroblastosis was not seen in those with sex-linked anemia, however, except in 1 case in which it followed splenectomy. There was decreased erythrocyte fragility in hypotonic

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saline solutions as might be anticipated with the degree of red cell distortion present. The ordinary anti-anemic measures proved to be of no therapeutic value, and in 1 case splenectomy, as in Cooley's anemia, was of no benefit. Several features may be cited which serve to differentiate the 2 types of anemia. Leukocytosis with immaturity of the myeloid cells, common in Mediterranean anemia, was not seen in any of the individuals with sex-linked anemia and evidence of increased red cell hemolysis, icterus, increased blood bilirubin and urobilinogen excretion, or high reticulocytosis was minimal or absent in all of the anemic males studied. Roentgenograms of the skeleton in those with the sex-linked anemia showed none of the abnormalities so characteristic of Mediterranean anemia when it is present in comparable severity.[2,6,20,43] The degree of splenomegaly and hepatomegaly, also, is far less in the sex-linked anemia than in similarly severe Mediterranean anemia. The difference in the genetic transmission of the 2 types of anemias has already been discussed.

A general classification or final description of the hereditary anemias is far from possible at this time. Evidence is accumulating to show that inherited abnormalities of erythrocyte formation or of hemoglobin production are probably more common than generally recognized.[4] A disorder of this type should be considered in diagnosis when in an otherwise healthy individual a hypochromic anemia does not respond to iron therapy, or where there is an unusual degree of red cell malformation with or without splenomegaly, hepatomegaly, or evidence of increased hemolysis. Errors in diagnosis may be made when such refractory anemias are attributed to chronic blood loss which cannot readily be demonstrated or patients may be unjustly accused of failing to take the prescribed iron medication. The hematologic findings are seldom entirely pathognomonic of an hereditary disorder, however, and examinations of other members of the family group, especially the parents, are often necessary before the etiology is entirely clear. In such investigations it may be anticipated from the heredity standpoint that a disorder having a given clinical appearance (phenotype) may be found to vary in its genetic basis of transmission (genotype) in different families or in different racial groups.

Summary. A hypochromic microcytic anemia with deformed erythrocytes, splenomegaly and sometimes hepatomegaly, affecting the male members of 2 families through several generations, has been described. The disease appears to be transmitted from generation to generation by females, many of whom have enlarged spleens and minor red blood cell abnormalities without anemia, in a manner compatible with sex-linked inheritance in which the abnormality is recessive, or incompletely recessive, in females.

The general problem of the atypical hereditary anemias is discussed.

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BLOOD CHANGES RELATED TO SULFONAMIDE THERAPY

I. Aplastic Anemia Associated With Sulfonamide Therapy

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Aplastic anemia as discussed in this report is regarded as a disease entity in which granulocytopenia, marked anemia and thrombocytopenia are associated with hypoplasia of the bone marrow. The rarity of the condition is evidenced by the paucity of reported cases. The disease occurs chiefly in young adults in a good state of nutrition, is refractory to treatment with any of the accepted hematopoietic agents and is invariably fatal except in some of the secondary group. Aplastic anemias are divided into 2 groups, idiopathic and secondary; the secondary group may be on an infectious, toxic or chemical basis. Six cases of aplastic anemia are reported here. In 5 of the patients there was a definite history of relationship to sulfonamide therapy and in the 6th the autopsy findings were indicative of similar therapeutic association. In 4 of the cases the clinical diagnosis was confirmed by autopsy findings. Arsenicals, Roentgen ray and ultraviolet radiations, gold preparations, phenol and sulfonamide drugs are the most common therapeutic agents producing this anemia, and benzene, toluene, anilin dyes and poisonous gases have also been implicated. Arsenical and benzene compounds have been the etiologic factors in the majority of the recorded cases. Blood dyscrasias are among the less frequently observed pathologic changes produced by the sulfonamides and include hemolytic anemia, aplastic anemia, granulocytopenia and purpura. Granulocytopenia associated with sulfonamide therapy will be discussed in the following paper. A moderate number of hemolytic anemias associated with sulfonamide therapy in adults has been recorded, but aplastic anemia due to these drugs has been uncommon and we have found only 3 cases in the literature. In 1942, Meyer and Perlmutter[2] reported the development of aplastic anemia in a 55 year old female following the administration of 12 gm. of sulfathiazole in the treatment of pneumonia. Discontinuance of the drug and repeated blood transfusions resulted in regeneration of the bone marrow, but the patient subsequently died of infection. Strauss[3] in 1943 described an erythrocytic aplasia following the administration of 11 gm. of sulfathiazole in a colored female aged 55 years. After 5 blood transfusions there was regeneration of bone marrow and the patient recovered. Sutliff and associates[4] investigating sulfonamide intoxication as a cause of death in New York City in 1941 reported 1 case of aplastic anemia among 8 deaths.

Pertinent data regarding the 6 patients who died recently from aplastic anemia in the Children's Hospital of Pittsburgh are outlined in the following pages.

Case Abstracts. Case 1. J. G., a white 13 year old male, was admitted to this hospital on Sept. 8, 1943. Past medical history was not pertinent. Nine weeks before admission the boy had been lacerated in the right side by a pitchfork and was given antitetanic serum immediately. He became anemic and sulfathiazole and ferric sulfate were administered for 9 days at home without any improvement. He was then admitted to Greene County Memorial Hospital

of Waynesburg with a diagnosis of aplastic anemia. Roentgen rays of the chest were negative. Urinalyses and repeated blood cultures were negative. Between August 17 and 27, 27 gm. of sulfadiazine were given. On August 26, the stool showed occult blood. After 8 blood transfusions and intensive antianemic therapy the patient had not improved and on September 8 was transferred from the Waynesburg Hospital to this hospital. The chief complaints were bleeding from ulcerated gums and mouth, epistaxis, blurred vision and subcutaneous hemorrhages. There were enlarged cryptic tonsils and an inflamed posterior pharynx. The lungs were clear. A diffuse precordial thrill was palpable over the heart and a harsh systolic apical murmur was heard. The clinical course was progressively downward and death occurred on October 4. The blood counts during the course of treatment are included in Table 1.

TABLE 1.—BLOOD EXAMINATIONS

Patient	Date	Hb. (gm.)	RBC$^{10^6}$	WBC$^{10^3}$	% granulocytes	Platelets$^{10^3}$	Other tests	Remarks
1. J. G.	7/15/43	4.5	1.3	2.0	39	86	....	In Waynesburg Hosp.
	7/30/43	7.0	2.0	2.0	46	89		
	8/30/43	5.0	1.5	1.0	9			
	9/ 8/43	4.9	1.1	1.1	3	44	Bleed. time 5′, coag. time 6′	In Children's Hosp.
	9/16/43	3.5	1.2	2.1	3	..	No reticulocytes	
	9/18/43	3.8	1.1	0.9	..	..	No reticulocytes	Transfusions
L. B.	4/ 3/42	14.0	4.5	10.0	52	..	....	First admission
	2/28/43	13.5	4.1	22.0	67	..	....	Second admission
	9/ 8/43	5.2	1.5	1.1	3	51	....	Third admission
	10/ 1/43	2.6	0.8	1.3	3	..	....	Repeated transfusions
3. A. T.	12/ 3/42	3.7	0.9	5.5	56	215	Bleed. time 1.5′, coag. time 10+′	Repeated transfusions
	12/15/42	8.8	2.6	4.0	27	..	Fragility normal	
	12/31/42	11.3	3.5	9.0	17			
	1/19/43	10.0	4.0	5.2	7			
	1/30/43	8.0	2.7	1.8	4			
	2/ 1/43	6.9	2.3	0.9	3			
4. D. L	1/ 8/45	*	0.8	2.2	15	66	Nucl. red cells, 41 to 100 WBC	
	7/ 9/45	13.0	4.1	5.6	50	..	....	Blood transfusions
5. J. M. R.	7/29/43	11.0	3.9	3.3	39	..	....	First admission
	8/10/43	9.5	3.0	3.9	14	..	....	Second admission
	8/16/43	12.8	4.4	1.4	46			
	11/23/43	2.7	0.9	0.7	15	54	Bleed. time 56″, coag. time 4′	Third admission
	11/29/43	6.8	1.5	0.5	3			
6. A. Z.	7/31/44	6.2	2.1	2.7	11	60	Bleed. time 6′, coag. time 3.5′	First admission, Uniontown Hosp.
	9/ 9/44	9.5	3.4	6.1	45			
	1/28/45	6.7	3.1	1.9	6	..	No reticulocytes, fragility normal	Second admission, Uniontown Hosp.
	3/ 3/45	8.5	2.6	2.1	32			
	3/15/45	6.5	2.4	1.9	6	18.6	....	In Children's Hosp.
	3/23/45	6.0	1.6	1.1	4	..	....	Repeated transfusions
	3/29/45	6.5	2.3	1.2	5			

* Too low to read.

Drug therapy prior to hospitalization included tetanus antitoxin, wet dressings of chloramine, ferrous sulfate and sulfathiazole (amount not obtainable) for 1 week. In the Waynesburg Hospital, 27 gm. of sulfathiazole were given.

At *autopsy* ($3\frac{1}{2}$ hours after death), the body showed small ulcerations and blood crusts around the mouth and nares. The subcutaneous tissues of the head, trunk and extremities were darkened with extravasated blood and petechiæ. On the right buttock, there was an abscess 6 cm. in diameter with 2 draining sinuses. Petechiæ were also present in the intercostal muscles, pleura, myocardium and stomach. The right lung contained numerous small abscesses. The softened liver extended 7 cm. below the costal margin in the mid-clavicular line and showed toxic central necrosis. Two areas of ulceration, each 2.5 cm. in diameter, were found in the terminal ileum which contained blood in the lumen. Grossly the kidneys were enlarged and showed hemorrhage in the pelves.

Anatomic Diagnoses: Aplastic anemia; terminal septicemia; multiple abscesses of right lung; toxic central necrosis of liver;

petechial hemorrhages of pleura, myocardium and stomach; ulceration of ileum; parenchymatous degeneration of kidneys; abscess of right buttock; aplasia of bone marrow.

Microscopic examination of *heart* showed edema and advanced parenchymatous degeneration. Passive congestion and emphysema were observed in the *lungs*. The *liver* showed fatty infiltration, serous hepatitis and toxic central necrosis. Marked parenchymatous degeneration of *kidneys* was present.

The *bone marrow*, which showed little hematopoietic tissue, consisted of loose interlacing threads of the walls of sinusoids containing an occasional nucleus. The nucleated blood cells which remained were mainly normoblasts and none of the myelogenous series could be recognized. A few large cells with vacuolated pink cytoplasm which may have been late megalocytes were seen. An occasional closed sinus was dilated with erythrocytes and rarely with developing late normoblasts.

Case 2. L. B., a 9½ year old white male, was admitted to this hospital the third time on Oct. 15, 1943, with a history of bruising for 6 weeks and vomiting blood. The child's first admission from May 5 to 12, 1941, was for the repair of a right indirect inguinal hernia and undescended testicle. The second admission from March 28 to April 5, 1942, was because of an acute bronchopneumonia. In the interim between the second and third admission, on Oct. 15, 1943, the child received 28 gm. of sulfathiazole and had a sulfathiazole bandage applied to the right leg for 4 days.

On the later date the child appeared acutely ill with blood crusts around the external nares and large ecchymoses on all extremities. The temperature was 100° F. and the pulse rate was 90 per minute. The anterior cervical and axillary lymph nodes were discrete and palpable. The lungs were clear but a systolic atypical murmur was heard. Blood examinations are recorded in Table 1. The clinical diagnoses were acute granulocytopenia and purpura of undetermined origin. Death occurred on October 17. The known *drug therapy* included 34 gm. of sulfathiazole and the application of a sulfathiazole bandage.

At *autopsy* (6½ hours after death) the left pupil was considerably dilated and blood crusts were present in the nares, mouth and right external auditory meatus. In the *skin* many ecchymoses were observed. The chest showed an enlarged *thymus*, petechial hemorrhages along the anterior coronary groove and extensive bronchopneumonia in both *lungs*, from which *Hemophilus influenzæ* was cultured. The *liver* extended 4 cm. below the right costal margin and showed central toxic necrosis. Partially digested blood was present in the *stomach*, *ileum* and *colon*. The Peyer's patches and solitary lymph follicles were enlarged. *Bone marrow* from the rib appeared pale and reduced in amount. Direct smears were devoid of granulocytes and contained only a few erythrocytes.

Anatomic Diagnoses: Aplastic anemia; multiple ecchymoses of skin; tracheobronchitis (*H. influenzæ*); bronchopneumonia; petechial hemorrhage of pericardium; massive hemorrhage into gastro-intestinal tract; toxic central necrosis of liver; parenchymatous degeneration of kidneys; Meckel's diverticulum; hypoplasia of bone marrow.

Microscopic examination showed irregularly distributed areas of bronchopneumonia. Chronic pericholangiitis, serous hepatitis and toxic central necrosis were observed in the *liver*, and parenchymatous degeneration was present in the *kidneys*. The *bone marrow* consisted of a network of fine red lines which represented the walls of sinusoids. A few closed sinusoids showed developing cells, most of which were late normoblasts. No cells of the granulocytic series, very few erythrocytes and a rare megakaryocyte were observed.

Case 3. A. T., a 3 year and 9 month old white male, was admitted to this hospital on Dec. 3, 1942. Three weeks previously the child had been in the Pittsburgh Municipal Hospital for 1 week with a tentative diagnosis of tonsillar diphtheria for which he received sulfanilamide (amount not obtainable) and 80,000 units of diphtheria antitoxin. Past medical history was negative. The child appeared pale and poorly nourished. A few small posterior cervical lymph nodes were palpable. The temperature was 103° F. and the pulse rate was 130 per minute. Physical examination revealed no abnormalities other than severe anemia with a questionable primary blood dyscrasia. On January 23 the gastric contents contained no free hydrochloric acid. The skull Roent-

gen ray showed no pathologic change. The blood counts are recorded in Table 1. Many transfusions of both plasma and whole blood increased the hemoglobin and red cell count but had little effect on the number of white cells, and just before death granulocytes completely disappeared from the circulation. A septicemia developed from multiple staphylococcic skin abscesses and death occurred on February 2.

Drug Therapy. An unknown amount of sulfanilamide and 80,000 units of diphtheria antitoxin were given in the Municipal Hospital. In our hospital pentnucleotides, yellow bone marrow and iron compounds were given for the anemia and sulfathiazole ointment was used for the skin abscesses.

At *autopsy* (1½ hours after death) widespread red maculopapules and pustules were present over the body. The tissues of the anterior *mediastinum* were infiltrated with fluid and both pleural cavities contained clear fluid. The *lungs* showed scattered areas of bronchopneumonia and a few small abscesses containing staphylococci and streptococci on the anterior surface. The *liver* extended 5 cm. below the costal margin and was dotted with small multiple abscesses which were also present in the kidneys and spleen. The *stomach* contained 50 cc. of coffee-ground mucoid fluid.

Anatomic Diagnoses: Aplastic anemia; bacteremia (staphylococcic); generalized embolic abscesses of lung, liver, kidney and spleen; bronchopneumonia (*H. influenzæ*); parenchymatous degeneration of kidneys; aplasia of bone marrow.

Microscopically both lungs contained patches of bronchopneumonia and multiple abscesses which consisted of necrotic tissue devoid of granulocytes. The *spleen*, *liver* and *kidneys*, likewise, showed many embolic agranulocytic abscesses. Serous hepatitis was also present in the liver. The *bone marrow* was hypoplastic and contained several small abscesses made up of clumps of staphylococci, almost no polys, and a dense peripheral zone of degenerating erythrocytes and nucleated red blood cells. The open sinuses were dilated with serum containing an occasional red cell and their walls appeared as thin red lines with an occasional nucleus. The closed sinuses formed a network of red staining threads, many of which were of double contour. Occasionally these were separated and distended with from 12 to 20 erythrocytes and a rare nucleated red cell. The walls showed an occasional developing erythrocyte. Practically no cells of the myelogenous series were recognized and only a rare megakaryocyte was noted.

CASE 4.—D. L., a 4½ month old emaciated white male was admitted to this hospital on Jan. 8, 1945, because of pallor and weight loss. The child, a 7 month baby at birth, was well until 1 month before admission when he developed a dry cough. On Dec. 23, 1944, iron was prescribed at home but he vomited frequently thereafter and lost weight. Several small shotty anterior cervical and axillary lymph nodes were felt. Over the base of the left lung there was decreased resonance. The heart was normal except for some tachycardia. The liver extended to the level of the umbilicus and the spleen was palpable. Diagnostic impressions were a blood dyscrasia of unknown origin and pneumonia of the left lower lobe. The blood cell values are included in Table 1. The illness ran a rapid course and the child died on Jan. 9, 1945.

Drug Therapy. The only obtainable history of drug therapy was that of iron medication.

At *autopsy* (2½ hours after death) many small petchiæ were noted over the surfaces of the *myocardium*, *lungs*, *liver* and *kidneys*. On section the lungs showed numerous patchy areas of bronchopneumonia. The liver had the mottled appearance of toxic central necrosis. Hemorrhage was present in the medulla of both *adrenals*. Smears from the *bone marrow* revealed a few erythrocytes, some normoblasts with a bluish or gray cytoplasm and an occasional neutrophil.

Anatomic Diagnosis: Aplastic anemia; bronchopneumonia; petechial hemorrhages of lungs, liver, heart and kidneys; fatty infiltration of liver; toxic central necrosis of liver; hypertrophy of spleen and hypoplasia of bone marrow.

Microscopically the *lungs* showed an interstitial pneumonia, chronic passive congestion, atelectasis and emphysema. Besides fatty infiltration and granular degeneration of the *liver* there was a central and focal toxic necrosis. The areas of focal necrosis closely resembled those which have been described from this laboratory in sulfonamide poisoning.[1] These areas were irregular in size and distribution, and showed varying degrees of necrosis and degeneration of liver

cells. Frequently such degenerating cells contained neutrophils. The central necrosis involved one-third to one-half of the lobule in which many hepatic cells exhibited marked loss of cytoplasm or had completely disappeared. The *spleen* contained areas of focal toxic necrosis, especially beneath the capsule. The *liver* and *spleen* exhibited extramedullary hematopoiesis. The sinusoids of the *lymph nodes* were dilated and contained many large macrophages with a reddish cytoplasm, probably due to ingested red blood cells. Parenchymatous degeneration was marked in the *kidneys* where a few small areas of focal necrosis occurred in the cortex.

Sections of *bone marrow of rib* showed hypoplastic tissue in which the walls of the sinusoids stained as reddish interlacing threads with reduced cellular formation. Almost no granulocytic cells were present. Here and there an occasional eosinophil as well as a rare neutrophilic myelocyte was noted. No megakaryocytes were encountered.

Case 5. J. M. R., a 6½ year old female, had 3 periods of hospitalization at this hospital, namely, July 7 to 12, July 28 to August 29 and November 23 to December 4, 1943. A diagnosis of rheumatic fever was made in March 1943. On July 7 a tonsillectomy was performed and the patient was discharged 5 days later. This operation was followed by an intermittent fever with chills which occasioned the second admission, during which time she received sulfadiazine. Repeated blood cultures were negative. Cultures of feces were also negative. Two weeks previous to the third admission the child developed pneumonia. At this time the cervical and inguinal lymph nodes were palpable. Breath sounds were diminished in the left base posteriorly and the heart was slightly enlarged. The pulse rate was rapid and there was an apical systolic murmur. Abdominal palpation was negative and the reflexes were physiologic. Urinalyses showed a faint trace of albumin. The blood counts are recorded in Table 1. Diagnostic impressions were rheumatic heart disease with mitral insufficiency and anemia with granulocytopenia. In spite of repeated transfusions and intensive anti-anemic therapy the illness ran a rapid course with gradual decrease in cellular blood elements. The patient died on December 4 with a diagnosis of aplastic anemia. Permission for *autopsy* was not obtained.

Drug Therapy. During the second hospitalization period, the child received 14 gm. of sulfadiazine and 2.6 gm. of sulfanilamide. Following this therapy, 17 gm. of a sulfa drug were given at home. Other treatment included anti-anemic medication and salicylates.

Case 6. A. Z., an 8 year old female, was admitted to this hospital on March 14, 1945, subsequent to 2 admissions to the Uniontown Hospital. During the first admission from July 31 to Sept. 11, 1944, the child received a sulfonamide drug for 2 days for a fever of unexplained origin. Repeated blood cultures and agglutination tests at that time were negative. The diagnoses were bilateral suppurative otitis media and aplastic anemia. On the second admission to the same hospital on Jan. 28, 1944, blood cultures were positive for hemolytic streptococcus. Roentgen ray pictures showed an irregular rarefaction of the left femur. The blood counts are tabulated in Table 1. On March 14, 1945, the patient was referred to this hospital. Physical examination revealed a pale, well-developed but poorly nourished child. Both ear drums were reddened. The mucous membranes were pale, the tonsils were hypertrophied, the pharynx was injected and the superficial lymph nodes were enlarged, discrete and non-tender. Examination of chest and abdomen were negative. Pain was elicited over both femurs and great toes on palpation. Blood transfusions and penicillin injections somewhat improved the blood picture (Table 1). A sternal marrow puncture on March 29 contained only mature red cells, lymphocytes and lymphoblasts although a few cells may have been questionable granulocytes. The blood picture suggested aplastic anemia. Repeated blood cultures were negative. During hospitalization, the temperature was septic in type and fluctuated between 98° and 107° F. The child ran a progressively downhill course and death occurred on April 7. Permission for autopsy was not obtained.

Drug Therapy. Prior to her first period of hospitalization this child was treated with a sulfonamide drug of which we could obtain neither the type nor the exact dosage. Following this therapy, she had 3 intensive courses of penicillin injections.

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Discussion. As we have previously indicated, aplastic anemia, especially in children, is of rare occurrence. In this hospital during the past 16½ years a total of 7 cases including the 6 reported in this paper has been encountered. The first of these 7 cases occurred between the years 1928 and 1942, inclusive, and was classified as idiopathic, as no definite etiologic factor could be found. The remaining 6 cases occurred in the 2½ years ending July 1945, and from the available clinical and pathologic evidence their origin, except in 1 case (Case 4), can be attributed to the sulfonamides administered. In Case 4 the pathologic findings implicated sulfonamides. Although the incidence of aplastic anemia during the last 2½ years has been markedly increased, it should be noted that many of these patients were referred to this hospital from outside the Pittsburgh area. The biennium and a quarter in which these aplasias developed has been marked by an extensive clinical use of sulfadiazine and sulfathiazole which have largely superseded the earlier prescribed sulfanilamide and sulfapyridine. These latter drugs, so far as our records are concerned, gave a lower incidence of blood dyscrasias. The size of the dose is important and many of the patients developed pathologic changes in the blood following high dosage, *e. g.*, 27 gm. of sulfadiazine and 34 gm. of sulfathiazole. It is often difficult to obtain an accurate history of the amount of drug and the duration of its use. The age incidence among the 6 children has ranged from 4½ months to 13 years, and sex does not appear to be an important factor. In the 4 cases in which autopsy tissues were examined the deleterious effect of the drug was not limited to the bone marrow and lesions were also found in the liver and other organs. It is worthy of note that, although there was considerable accompanying liver damage, jaundice and renal manifestations rarely were observed with sulfadiazine as had been the case in this hospital previously with sulfapyridine. The bone marrow sections of aplastic anemia indicated an almost complete loss of all hematopoietic cells and especially the primitive cells lining the sinusoids, which picture suggested that the deleterious effect of the drug occurs primarily in the endothelial lining of these channels.

The bone marrow of children is apparently much more labile and susceptible to the toxic action of the drug than that of adults; hemolytic rather than aplastic anemia has been more frequently recorded in grown individuals. Because this condition is frequently associated with preëxisting infection, particularly of the upper respiratory tract, it is believed that the bone marrow as well as other tissue may have been depleted of enzyme by bacterial toxins early and thus rendered more susceptible. The pathogenesis of the lesions resulting from the action of the drug may possibly be on the basis of an acquired hypersensitivity, although we are inclined to interpret them as a direct interference with the utilization of enzymes which are concerned in the development and maturation of the various cells of the bone marrow. The sensitivity theory has for its support the fact that repeated series of dosage are found in some of the cases. A basis for the second or direct tissue impairment theory lies in the fact that most of the patients have a history of previous or concomitant infection. Data considered in a later paper related to the treatment of the sulfonamide granulocytopenia would confirm the belief that the pathogenesis lies in the interference of enzymes necessary to the development of the marrow. This view brings up the question as to whether the sulfonamides have an equally injurious and inhibitory effect upon the anlage of the red blood cells, of the neutrophil and of the platelet, and at what point in each of the developing series the sulfonamide exerts its initial toxic action. The anlage of the neutrophil is apparently more susceptible than that of the other 2 series. Sections of bone marrow from patients with aplastic anemia and with granulocytopenia would indicate the point

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of attack to be on the early and more primitive cells of the series. Further evidence of this belief is the observation that in the restitution of the maturation process by enzymic therapy there is little increase in the reticulocytes. As is known, the protoporphyrin which characterizes the reticulum of the red cell is incorporated in the early stages of the developing cells, and persists only in cells whose maturation has been delayed, and which are subsequently released into the circulation upon treatment.

Summary. In 4 of 6 described cases of aplastic anemia associated with sulfonamide therapy, bone marrow sections taken at autopsy revealed an extensive hypoplasia. The depletion of hematopoietic tissue is interpreted as resulting from direct injurious action of the drug on the early developing cells of the marrow.

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BLOOD CHANGES RELATED TO SULFONAMIDE THERAPY

II. Granulocytopenia Associated With Use of Sulfonamides

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In the preceding paper, 6 cases of aplastic anemia occurring in patients in this hospital during the past 2½ years were described. The fact that these aplasias were associated with sulfonamide therapy early suggested that a series of progressive granulocytopenias related to the use of these drugs might also be found. During the first 3 months of 1944 and 1945 the blood counts of patients were followed with particular reference to granulocytopenias developing during treatment with the sulfonamides. It was found that during 1944 there was a high incidence of neutropenias and that in the following year, when penicillin treatment had replaced much of the sulfonamide therapy, this incidence had been reduced almost one-half. The blood counts which each patient receives in the hospital have for many years been made and tabulated daily by 2 members of the laboratory staff, thus it was possible to make a comparison of the number of granulocytopenias studied in 1944 and 1945 with those listed from 1936 to 1943 inclusive. This comparison revealed that previous to the introduction of sulfonamide medication into the hospital wards in 1940, the incidence of granulocytopenias averaged 3% of the number of admissions and in the years following there was a gradual increase which reached a maximum of 12% in 1944 when the use of sulfadiazine was at its peak. The varying incidence of granulocytopenias in relation to the sulfonamides is discussed in the following pages.

Reports in the Literature. Coincidental with the clinical use of these drugs, reports have been published of their toxic effects, among which latter are a moderate number of granulocytopenias. The first mention of leukopenia associated with sulfonamide therapy, which we have found, is that by Young,[31] who in 1937 described this condition developing in a patient following the use of sulfanilamide. In 1938, Lloyd, Erskine and Johnson[19] noted 4 cases of moderate granulocytopenia in 36 adults treated with sulfapyridine. In 7 children given this drug for gonococcic infections, 1 child developed a mild granulocytopenia. Kracke[18] has collected 6 other references for 1937 in which agranulocytosis followed the administration of sulfanilamide. In 1939, Morgan and Detweiler[23] treated 76 patients suffering from pneumonia with sulfapyridine and observed leukopenia in 8 individuals, 1 of whom died. In 1941, Rinkoff and Spring[26] reported 6 cases, with 2 deaths, illustrating myeloid depression occasioned by sulfanilamide and sulfapyridine. Kennedy and Finland[16] described an agranulocytosis in a patient with endocarditis treated with sulfathiazole, and these authors[8] also reported a fall in the leukocyte count below 4000 cells per c.mm. in 9 out of 146 persons treated with sulfadiazine. Long, Haviland, Edwards and Bliss[20] found 0.4% leukopenias in 1000 patients receiving sulfanilamide, 0.9% among 297 patients receiving sulfapyridine and 1.6% among 271 patients receiving sulfathiazole. Flippin, Rose, Schwartz and Domm[11] listed a total of 2% leukopenias with sulfadiazine, as compared with 3% following sulfathiazole in 200 treated patients. Finland, Peterson and Goodwin[9] found 3 granulocytopenias below 4000 per c.mm. among 460 patients receiving either sulfadiazine or sulfathiazole. Sutliff and

associates,[29] investigating sulfonamide intoxication as a cause of death in New York City in 1941, recorded 8 cases of agranulocytosis among 28 deaths following the use of various sulfonamide compounds. Hall and Spink[13] treated 116 patients with sulfamerazine and noted 1 case of leukopenia. In a survey of hematology for 1943, Bethell, Sturgis, Mallery and Rundles[4] collected 19 published cases of agranulocytosis due to various sulfonamide compounds. In a study of the results of the treatment of 186 patients with different sulfonamides, Frist[12] described 3 cases of agranulocytosis with 2 deaths. Vilter and Blankenhorn[30] analyzed 116 toxic reactions, including 2 cases of agranulocytosis resulting from the use of the newer sulfonamides, on 1936 patients during the 4 years ending with 1944. In a study of 1357 patients, Plummer and Wheeler[25] found 15 cases of granulocytopenia. Various authors have reported single cases of leukopenia with different sulfonamide compounds and a few of these are appended. An unusual case of fatal agranulocytosis following intraperitoneal implantation of 5 gm. of sulfanilamide was described by Arrowsmith, Binkley and Moore.[1] Favorite, Reiner and London[7] reported a case of leukopenia due to sulfamerazine and Sutherland[28] 1 due to sulfanilamide. Park,[24] Blue,[5] and Koteen[17] each described a case following sulfadiazine, and Baker and Fenner[2] observed another case following sulfapyridine.

Only a few publications on retrograde changes occurring in the blood of children treated with sulfonamides have appeared. The report of Lloyd *et al.*[19] has already been cited. Barlow[3] observed agranulocytosis 7 days after the ingestion of 1.25 gm. of sulfapyridine in an infant 1 year and 7 months old, and Kato and associates[15] noted a case of fatal agranulocytosis after sulfathiazole treatment in an infant 8 weeks old. Three cases of agranulocytosis following sulfapyridine, 2 of which were fatal, were described by Rosenthal and Vogel.[27] Herlitz[14] recorded a 4% incidence of granulocytopenia following the use of sulfathiazole and showed that in 3 children there was an accompanying myeloid depletion of the bone marrow. Fischer and Agerty,[10] in 2 papers, stated they found no marked change in the blood of children treated for pneumonia with sulfapyridine and sulfathiazole. On the other hand, Dowrie and Abramson[6] found 24 cases of granulocytopenia in 54 sulfadiazine treated children (44%) and 20 cases in 53 sulfathiazole treated children (38%).

Results and Discussion. A cursory survey of the daily counts with the patient's name listed during 1942 and 1943 in this hospital indicated that the incidence of granulocytopenias was highest in the first 3 months of the year, during which period upper respiratory infections were most frequent. The blood counts as they were recorded daily during each first quarter of the years 1944 and 1945 were, therefore, chosen for a study of the frequency of blood changes referable to retrograde myeloid changes associated with sulfonamide therapy. Our series includes the granulocytopenias of 3000 or less granular cells per c.mm. developing in children during these 2 periods. Patients suffering from pertussis, leukemia and conditions definitely unrelated to sulfonamide therapy were excluded. Special effort was made to secure complete histories, especially of previous medication, and considerable difficulty was frequently encountered in obtaining information concerning sulfonamide therapy before admission of the patient to this hospital. For the past 4 years the morphologic blood work has been under the direct supervision of one of us (E. G.), who has made most of the differential counts.

The data collected during 1944 and 1945 are epitomized in the latter parts of Tables 1 and 2. The 125 instances of low leukocyte counts tabulated from Jan. 1 to April 1, 1944, occurred among 1021 admissions, that is, 12% of the total number of patients. The 79 instances of low leukocyte counts found during the same period in 1945 occurred among 1039 admissions, or 7.6% of the total number of patients.

In 1944, approximately 650 patients received sulfonamides, of which number 125 (19%) developed neutropenia. In 1945, approximately 360 patients received sulfonamides and of this number 79 (21%) developed neutropenia. By actual statistical count the 125 granulocytopenias in

1944 fell to 79 in 1945, although the total number of patients admitted to the hospital in these 2 years was practically the same. This reduction of 40% was due to partial replacement of sulfonamide therapy in the latter year by penicillin. In contrast, however, the percentage of myeloid depressions due to administered sulfonamides in each of these 2 years remained practically the same. The percentage of granulocytopenias in this biennial period were equal, affecting about 20% of all children receiving the drug.

The fact that the total number of children developing agranulocytosis in 1945 was about half as great as that in the previous year requires some comment. Several factors may have been responsible. First, as already noted, in 1945 many patients received penicillin in place of the sulfonamides and it has been our experience that little or no depression of hematopoietic activity is caused by penicillin, a fact noted by other workers. Secondly, there was some change in the type of upper respiratory infections in the latter year. In 1945, there was a predominance of influenzal tracheitis, fewer typical childhood pneumonias and a moderate number of atypical pneumonias. Furthermore, the duration of treatment of many children with the sulfonamides was limited to 2 or 3 days, and often then replaced by penicillin. A considerable number of milder leukopenias with a count slightly higher than 3000 cells per c.mm. occurred but these are not included because they lie in the range of physiologic variations. The percentages obtained by us for neutropenias developing with the use of sulfonamides are of lower value than the incidence of 38% and 44% found by Dowrie and Abramson,[6] but these authors studied a more or less selected group of patients and our series represents consecutive unselected cases. Repeated blood examinations made on many of the leukopenic children who at our request were brought back to the dispensary 2 weeks after their discharge for a check-up blood count disclosed that the blood of a number had acquired a normal complement of cells during that time. In 22 patients in the 1944 series, whose white blood cell count did not become normal within 2 weeks after discontinuance of the drug, examinations were repeated 6 and 9 months later, and 10 of the 22 continued to have granulocyte counts of 3000 or less per c.mm., and 5 others had granulocyte counts between 3000 and 4000 per c.mm. The total number of the persisting granulocytopenias could not be accurately determined but the above observation would seem to indicate a significant number of children treated with sulfonamides, about 40%, had acquired a more or less permanent disturbance of the myelogenous mechanism. This finding confirms our conviction previously stated,[21] that repeated courses of sulfonamide medication tend to establish a lower pharmacologic resistance possibly the basis of what has been designated "drug sensitivity."

Having established by detailed study of consecutive individual cases the number of neutropenias developing in 1944 and 1945, we were interested in ascertaining by compilations made from blood counts listed in files of earlier years the number of similar granulocytopenias occurring previously. The data obtained for the 5 years ending in 1940 previous to the general use of the drug, through the years 1940 with small amounts and 1941 with a moderate supply of sulfapyridine, as well as for 1942 and 1943 with an increasing usage of sulfadiazine are included in Table 1. It should be mentioned that a limited amount of sulfapyridine was used during 1938 and 1939 in a study[22] of the effects of this drug on childhood pneumonia. In the 5 years preceding the introduction of sulfonamide medication the number of neutropenias per year averaged about 3% (Table 1). We could not determine the cause of the high percentage in 1937 and the low percentage in the succeeding year. In 1941 and 1942 the first biennium in which sulfapyridine was used, but in relatively moderate

TABLE 1.—FREQUENCY OF GRANULOCYTOPENIA DEVELOPING DURING JANUARY, FEBRUARY AND MARCH 1936 TO 1945 INCLUSIVE

	1936	1937	1938	1939	1940	1941	1942	1943	1944	1945
Patients admitted to hospital	494	684	768	765	812	797	958	1003	1021	1039
Patients developing granulocytopenia	20	31	7	26	41	62	67	104	125	79
% of granulocytopenias	4.0	4.5	0.9	2.9	3.8	7.7	7.0	10.3	12.0	7.6

TABLE 2.—AGE INCIDENCE OF DIFFERENT GRADES OF GRANULOCYTOPENIAS OCCURRING FROM 1931 TO 1945 INCLUSIVE

	Age									
	3 mos. or less	3 to 6 mos.	6 to 9 mos.	9 to 12 mos.	12 to 18 mos.	18 to 24 mos.	2 to 4 yrs.	4 to 6 yrs.	6 to 12 yrs.	Total
1936:										
I										
II										
III	..	..	..	..	..	..	1	1	1	3
IV	1	4	1	1	1	..	8	..	1	17
1937:										
I										
II	1	..	..	..	..	..	..	..	..	1
III	1	2	3	1	1	1	1	1	2	13
IV	1	3	2	1	5	1	2	1	1	17
1938:										
I										
II										
III	..	..	..	..	..	..	..	..	1	1
IV	3	3	..	..	..	..	..	..	..	6
1939:										
I										
II										
III	..	2	..	..	..	..	..	..	1	3
IV	4	5	4	1	1	1	2	2	3	23
1940:										
I										
II										
III	2	2	..	..	2	..	2	..	5	13
IV	4	4	1	..	2	2	6	6	3	28
1941:										
I										
II	..	1	..	..	1	..	..	..	..	2
III	1	3	2	2	4	1	1	3	2	19
IV	3	3	7	3	9	5	4	3	4	41
1942:										
I	..	1	..	..	..	..	..	..	1	2
II	..	..	..	..	1	..	..	..	..	1
III	1	2	2	5	3	..	3	1	3	20
IV	4	8	6	2	2	7	7	2	6	44
1943:										
I	..	..	2	..	..	..	..	..	..	2
II	..	..	2	..	1	..	1	1	..	5
III	4	6	6	1	8	3	8	2	3	41
IV	3	11	4	5	12	3	11	1	6	56
1944:										
I	2	..	..	..	..	..	..	..	..	2
II	..	1	1	..	2	..	1	1	..	6
III	..	2	3	1	7	3	15	9	10	50
IV	1	4	4	2	6	6	20	9	15	67
1945:										
I										
II	..	..	3	..	..	1	1	..	..	5
III	2	2	1	7	4	..	9	2	3	30
IV	4	2	2	5	12	3	6	2	8	44

I, white cell count containing less than 500 granulocytes per c.mm.
II, white cell count containing between 500 and 999 granulocytes per c.mm.
III, white cell count containing between 1000 and 1999 granulocytes per c.mm.
IV, white cell count containing between 2000 and 3000 granulocytes per c.mm.

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amount, the number of leukopenias rose to more than double this figure. In the biennium of 1943 and 1944 the clinical use of sulfadiazine reached a maximum with smaller amounts of sulfathiazole being prescribed. The rising incidence of the leukopenias from 1941 to 1944 inclusive undoubtedly paralleled the augmented use of the drug.

Furthermore, with the greater clinical use of the drug, there appeared for the first time in 1941 neutropenias below 1000 cells per c.mm. (Table 2) and in the following 3 years, as the cases with prescribed drug multiplied, neutropenias below a count of 500 per c.mm. were encountered. This latter group of exaggerated neutropenias was absent in 1945, as the sulfonamides were gradually superseded by penicillin. Age distribution as displayed in Table 2 apparently signifies that age *per se* is not a factor influencing frequency.

A survey of the hemoglobin and red blood cell counts of children, whose blood exhibited granulocytopenia, did not usually reveal an accompanying anemia. When a fall in the red blood cell counts was manifest, it occurred later in treatment than the neutropenia, and was of less intensity. In a few patients on whom platelet counts were made concomitantly these elements appeared, likewise, to be more resistant than the granulocytes to the deleterious action of the sulfonamide. Sternal punctures, as well as bone marrow, obtained at autopsy in a few patients showing neutropenia but dying from other causes, also indicated that the susceptibility of the early myeloid elements to the toxic action of the sulfonamides is greater than that of the precursors of the red blood cell and platelet. The relative frequency of low granulocyte counts in children would denote a greater instability of bone marrow in relation to sulfonamides in young individuals than in adults.

Because, in the cases studied in 1944 and 1945 the relative quantities of the 4 types drug used, namely, sulfanilamide, sulfapyridine, sulfadiazine and sulfathiazole, could not be accurately determined, it has not been possible to decide whether there is any appreciable difference in the extent of their individual injurious action on bone marrow. The reduced conjugation *in vivo* and the related more prolonged maintenance of high blood level of the 2 latter mentioned preparations, in contrast to the first 2, may be a significant factor in the increased incidence of granulocytopenias reported here.

Summary. In an analysis of the granulocytopenias with less than 3000 cells per c.mm. occurring in the first quarter of the years from 1936 to 1945 inclusive, an average frequency of 3% of the number of admissions found before the use of the sulfonamides was followed by a gradually increasing incidence which paralleled the augmented use of the drug. The incidence reached a maximum of 12% in 1944 when sulfadiazine medication was at its peak and diminished to 7.6% in 1945 when penicillin replaced much of the sulfadiazine. The percentage of neutropenias developing from sulfonamides in these 2 years, however, remained the same, namely, about 20% of all patients receiving the drug.

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BLOOD CHANGES RELATED TO SULFONAMIDE THERAPY

III. Treatment of Granulocytopenia With Folic Acid and Pyridoxine Hydrochloride

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The deleterious effects of sulfonamide compounds on the hematopoietic tissues of certain susceptible individuals has stimulated an interest not only in the elucidation of the factors concerned in the pathogenesis of the retrograde processes, but also in possible means of counteracting or correcting the bone marrow damage. Granulocytopenia and aplasia of bone marrow have in the past 4 years been produced experimentally in laboratory animals by the addition of known amounts of various sulfonamides to purified rations. In 1942, Daft, Ashburn and Sebrell,[5] and Daft, Ashburn, Spicer and Sebrell[6,27] recorded the occurrence of granulocytopenia and anemia in white rats when sulfaguanadine and succinylsulfathiazole were fed with controlled diets, and in the following year Axelrod, Gross, Bosse and Swingle,[1] and Daft and Sebrell[7] reported similar results. Kornberg, Daft and Sebrell[19] repeated these experiments with sulfadiazine and sulfathiazole. The blood changes found in the sulfonamide treated rats were comparable to those observed by Wilson, Doan, Saslaw and Schwab,[31] and Waisman and Elvehjem[30] in monkeys and by Campbell and associates[2] in chicks when these animals were fed with controlled diets, deficient in a factor which could be chemically separated from liver, yeast and spinach and with a widespread distribution such as in meat, soy bean, grass, oats and many other substances including bone marrow. This factor has been variously designated vitamin B_c,[15] folic acid,[21] *Lactobacillus casei* factor,[25,28] norite eluate factor[16,17] and *Streptococcus lactis* R factor,[21] depending upon the source, preparation and method of assay. The vitamin M of Day and his co-workers[8,9,10,11,20] is another designation for an identical substance.[12] The restoration of normal blood values in the 2 groups of experimental animals, namely, sulfonamide treated and "folic acid" deficient, by administration of concentrated liver fractions or norite eluate of liver extracts, both of which apparently owed their activity to the presence of "folic acid," strongly implicated this enzyme as a basic factor in the underlying pathologic change of the bone marrow. Wright and Welch[32] suggested that succinylsulfathiazole owes its injurious effects to a specific inhibitory action on certain enzyme systems, and Elvehjem[13] in 1943 hypothecated that the blood dyscrasias arising in sulfonamide treated patients might be due to an interference with "folic acid" metabolism by the drug. Sharp *et al.*[24] tested such a hypothesis by the use of vitamin B_c in 5 patients with anemia but obtained only a slight response.

In April 1944 we had the opportunity of trying a liver powder* containing 34 micrograms of *L. casei* factor per gm. for its effect in alleviating the neutropenia developing in children following the ingestion of sulfonamide. This powder was

* This liver powder and the preparations of *L. casei* factor were kindly supplied by Dr. T. H. Jukes of Lederle Laboratories, Inc., Pearl River, New York.

somewhat bulky and occasionally produced abdominal cramps in children when it was given to them in large amounts. The efficacy of this preparation in restoring blood counts to normal was tested on several patients in the Children's Hospital of Pittsburgh suffering from granulocytopenia following sulfonamide therapy, and also on a young woman who had aplastic anemia due to the sulfadiazine. Treatment gave no beneficial response in the latter person, and only slight temporary improvement in the blood count of the children. Early in 1945 we were supplied with a more purified liver concentrate in capsules, each of which contained 40 micrograms of *L. casei* factor. The dosage prescribed was 1 capsule 3 times a day regardless of the age of the patient. Infants and young children who could not swallow the capsule were given the contents in milk or other fluids. This concentrate produced little change in the leukocyte counts of 2 children after administration for more than 2 weeks.

In April 1945, we were supplied with a second lot of liver concentrate in capsules, each of which contained 48 micrograms of *L. casei* factor. The negative results obtained with the first sample of *L. casei* factor made us feel that possibly a second factor or enzyme might be involved in the development of the blood dyscrasias associated with sulfonamides. The conclusion of Hill, Norris and Heuser[14] from experiments on chicks that another factor besides folic acid was necessary for the prevention of anemia produced by purified diet was supported by the finding of Scott *et al.*,[22] that *L. casei* factor and a lactone derived from pyridoxine were required to prevent anemia developing in these birds fed on insufficient rations. Scott, Norris, Heuser and Bruce[23] showed that either one of the two lactones of pyridoxine, designated α pyracin and β pyracin, in combination of *L. casei* factor was more effective in preventing anemia in chicks than any one of the three substances used alone. Although a considerable literature on possible deficiency factors concerned with anemia has accumulated, only a few references related to deficiency neutropenias are available. Intravenous injections of pyridoxine were credited with creating an increase in the granulocytic series, as well as improving the anemia, by Vilter, Schiro and Spies[29] in 2 patients with pernicious anemia, whose blood also showed a neutropenia. Cartwright and associates[4] described a terminal leukopenia in 2 pigs fed on casein hydrolysate plus additions of vitamins and lacking pyridoxine hydrochloride but did not ascribe much significance to its occurrence. Cantor and Scott[3] obtained good clinical results in a case of sulfathiazole neutropenia by the intravenous daily injections of 125 to 200 mg. of pyridoxine for 6 days, a finding which induced us to supplement the *L. casei* factor with this medicament. Pyridoxine hydrochloride in amounts of 50 mg., 3 times a day by mouth, was added to the daily prescribed *L. casei* factor. This report analyzes the results of treatment for neutropenia in 23 patients, including 22 children and 1 adult, a nurse. Nineteen patients have been given *L. casei* factor combined with pyridoxine and 4 patients *L. casei* factor alone. Of this number, 14 individuals have shown a considerable rise in the percentage of neutrophils (Table 1). The remaining 9 children, some of whom received inadequate dosage, responded less favorably (Table 2). The duration of the treatment which was from 3 days to 1 month has been determined largely by the speed of the neutrophil response and by length of time the patient remained in the hospital. Of the successfully treated patients, 2 require comment. The patient, L. K., No. 13, was hospitalized for a staphylococcic infection in the axilla and a cellulitis which had spread along the right arm. This infection was fairly persistent and the boy received a large amount of sulfadiazine together with penicillin for 3 weeks, when the leukocyte count fell suddenly. This patient was then treated in the hospital with penicillin together with the folic acid and pyridoxine for a couple of weeks, when the leukocyte

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TABLE 1.—NEUTROPENIAS RESPONDING FAVORABLY TO L. CASEI FACTOR AND PYRIDOXINE HYDROCHLORIDE TREATMENT

Patient	Color	Sex	Age	Clinical diagnosis	Sulfonamide used	Duration of sulfonamide therapy, 1945	Amount of drug (gr.)	Penicillin (10^3 units)	Date of blood count	Hemoglobin (gm.)	RBC (10^6)	WBC (10^3)	Granulocytes (%)	Treatment	Duration of treatment
1. J. S.	W	M	4 mos.	Chronic bronchitis Enlarged thymus	D*	2-8 to 2-11	76	+ Roentgen ray, radium	I: 2-12 II: 2-14 III: 2-26 IV: 8-20	11.2 .. 12.0 10.5	3.80 .. 4.20 3.80	12.4 10.6 8.0 10.6	23 23 60 40	Folic acid Pyridoxine	2-14 to 2-26 12 days
2. P. S.	W	F	4 mos.	Allergic dermatitis	†	...	..	....	II: 2-26 III: 3-19 IV: 7-20	10.2 11.0 11.8	3.65 3.50 3.90	12.4 9.4 11.2	18 54 45	Folic acid	2-9 to 2-24 5 days
3. P. M.	W	F	5 mos.	Nasopharyngitis	D	6-10 to 6-15	82	205	I: 5-30 II: 6-6 III: 6-19	10.0 13.0 12.8	3.55 4.40 4.15	11.2 10.3 14.2	45 23 54	Folic acid Pyridoxine	6-7 to 6-20 13 days
4. J. M.	W	M	6 mos.	Chronic sinusitis Rickets	D	6-23 to 6-24	34	210	I: 2-23 II: 3-3 III: 3-10	11.5 11.8 12.0	4.30 4.01 4.00	22.6 10.8 10.0	28 23 67	Folic acid Pyridoxine Brewer's yeast	3-7 to 3-10 3 days
5. C. L.	W	M	5 mos.	Bronchitis Pharyngitis Leukopenia	†	..	..	....	I: 3-4 II: 3-9 III: 3-30 IV: 8-3 V: 8-31	12.5 .. 13.0 12.0 13.2	4.00 .. 4.30 4.20 4.40	6.4 7.1 14.0 7.6 7.2	24 14 66 55 62	Folic acid Pyridoxine Brewer's yeast	3-9 to 3-17 8 days
6. D. S.	W	F	6 mos.	Bronchitis	D	2-13 to 2-26	173.2	360	II: 2-13 III: 3-19	10.2 11.0	3.65 3.50	7.6 9.4	19 54	Folic acid Pyridoxine	3-11 to 3-19 8 days
7. M. B.	W	F	8 mos.	Bronchitis Otitis media	D	2-25 to 2-26	20	....	I: 2-25 II: 2-28 III: 3-12 IV: 7-20	10.0 11.0 11.8 10.8	3.40 3.75 4.00 3.70	4.5 7.4 10.4 8.1	24 19 55 40	Folic acid Pyridoxine Brewer's yeast	2-27 to 3-7 8 days
[illegible]				[illegible]					IV: 7-24	11.7	3.80	6.3	53	Pyridoxine Brewer's yeast	10 days
9. T. R.	W	M	16 mos.	Bronchopneumonia Otitis media	D T	2-6 2-7 to 2-12	25	13	I: 2-6 II: 2-16 III: 2-20	13.0 11.8 ..	4.35 4.20 ..	13.8 8.2 15.2	60 27 68	Folic acid	2-17 to 2-20 3 days

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7. M. B.	W	F	8 mos.	Bronchitis Otitis media	D	2–25 to 2–26	20	....	I: 2–25 II: 2–28 III: 3–12 IV: 7–20	10.0 11.0 11.8 10.8	3.40 3.75 4.00 3.70	4.5 7.4 10.4 8.1	24 19 55 40	Folic acid Pyridoxine Brewer's yeast	2–27 to 3–7 8 days				
8. [illegible]									III: 3–19	11.0	3.50	9.4	54	Pyridoxine	8 days				
9. T. R.	W	M	16 mos.	Bronchopneumonia Otitis media	D T	2–6 2–7 to 2–12	25	13	I: 2–6 II: 2–16 III: 2–20 IV: 7–27 V: 8–9	13.0 11.8 .. 13.0 12.2	4.35 4.20 .. 4.30 ..	13.8 8.2 15.2 11.3 9.9	60 27 68 67 44	Folic acid	2–17 to 2–20 3 days				
10. C. J.	B	M	20 mos.	Bronchopneumonia	D	6–9 to 6–14	69	....	I: 6–9 II: 6–13 III: 6–19	11.0 11.0 10.5	3.75 3.65 3.60	16.5 4.5 8.6	78 29 60	Folic acid Pyridoxine	6–15 to 6–21 6 days				
11. D. B.	W	M	2 yrs.	Bronchopneumonia	D	4–9 to 4–11	62	....	II: 4–9 III: 4–16 IV: 7–27	11.7 11.0 13.0	3.85 4.15 4.40	8.4 11.8 9.3	26 64 31	Folic acid Brewer's yeast Pyridoxine	4–10 to 4–15 5 days				
12. C. E.	W	M	3 yrs.	Tracheobronchitis	D	1–24 to 1–26	68	....	II: 2–24 III: 3–14 IV: 8–29	10.5 12.0 11.5	3.45 3.95 3.76	4.2 7.0 9.2	15 63 57	Folic acid	7 days				
13. L. K.	W	M	6 yrs.	Cellulitis, right arm and axilla	D	5–3 to 5–19	790	820	I: 5–3 II: 5–22 III: 6–21 IV: 7–21 V: 8–31	13.0 11.5 12.0 12.0 13.0	4.70 3.75 3.85 3.80 4.40	21.4 5.3 6.6 7.9 6.5	92 7 66 63 64	Folic acid Pyridoxine	5–21 to 6–21 31 days				
14. E. P.	W	F	22 yrs.	Infectious hepatitis	D	6–6 to 6–7	48	930	I: 6–6 II: 6–8 III: 6–21	14.0 11.8 12.2	4.55 3.85 4.10	2.2 4.3 4.8	79 36 72	Folic acid Pyridoxine	6–18 to 6–30 12 days				

* Sulfadiazine. † Type and amount of sulfonamide used not available. ‡ Sulfathiazole. § Amount of sulfonamide used not available.
I, Blood count before sulfonamide given in hospital. II, Blood count at peak of the granulocytopenia. III, Blood count after treatment with *L. casei* factor and pyridoxine. IV, Blood count made later. V, Blood count made later. When I is omitted the leukocyte count which was identical was depressed when patient was admitted to hospital because of previous sulfonamide therapy.

TABLE 2.—NEUTROPENIAS LITTLE ALTERED BY L. CASEI FACTOR AND PYRIDOXINE HYDROCHLORIDE TREATMENT

Patient	Color	Sex	Age (mos.)	Clinical diagnosis	Sulfonamide used	Duration of sulfonamide therapy, 1945	Amount of drug (gr.)	Penicillin (10^3 unit		Date of blood count	Hemoglobin (gm.)	RBC (10^6)	WBC (10^3)	Granulocytes (%)	Treatment	Duration of treatment
1. W. L.	W	M	1½	Tracheobronchitis	D*	2-22 to 2-23	15.0	..	I:	2-23	12.2	3.95	8.8	27	Folic acid	2-24 to 3-2
									II:	3-1	..	..	9.2	21	Pyridoxine	6 days
									III:	..	..	..	14.0	29	Brewer's yeast	
2. G. H.	B	M	2	Bronchopneumonia	D	4-8 to 4-10	34.0	..	I:	4-8	8.0	2.90	5.6	52	Folic acid	4-12 to 5-1
									II:	4-11	10.0	3.40	8.4	26	Pyridoxine	18 days
									III:	5-1	12.8	4.25	12.4	26		
3. C. H.	B	M	3	Bronchopneumonia	D	4-3 to 4-5	64.0	..	II:	4-3	10.0	3.65	11.0	29	Folic acid	4-4 to 4-10
									III:	4-10	12.8	4.25	8.0	41	Pyridoxine	6 days
4. C. F.	B	F	7	Bronchitis	D	3-14	39.0	..	II:	3-14	7.8	3.20	2.6	17	Folic acid	3-16 to 3-22
									III:	3-22	..	..	6.9	43	Pyridoxine	6 days
									IV:	7-20	9.0	3.60	7.2	42		
									V:	9-7	7.5	3.60	7.7	64°		
5. G. S.	W	M	12	Pharyngitis Chronic tonsillitis	D	†	..	..	II:	1-16	10.5	3.50	6.0	21	Folic acid	1-20 to 1-22
									III:	1-29	9.5	3.55	5.6	22	Pyridoxine	2 days
6. R. C.	W	M	14	Tracheobronchitis	D	2-13 to 2-19	213.0	105	I:	2-12	10.2	3.45	10.0	75	Folic acid	2-28 to 3-3
									II:	2-20	9.5	3.20	7.0	43		3 days
									III:	3-20	12.0	3.85	9.0	36		
7. J. K.	W	M	15	Tracheobronchitis	D	3-25 to 3-28	55.5	..	I:	3-25	11.5	3.75	7.2	40	Folic acid	2-30 to 4-1
									II:	3-28	9.5	3.62	6.5	27	Pyridoxine	2 days
									III:	3-29	..	..	9.5	45		
8. K. Z.	W	F	18	Bronchopneumonia	D	2-11	12.0	2455	I:	2-2	9.7	3.45	13.8	68	Folic acid	3-2 to 3-12
									II:	2-28	10.5	3.45	14.0	22	Pyridoxine	10 days
									III:	3-12	11.0	3.55	17.1	49	Brewer's yeast	
9. L. L.	B	M	18	Bronchitis Tonsillitis	D	1-15 to 1-16	78.0	..	I·	1-15	11.8	3.75	6.2	61	Folic acid	1-29 to 2-10
									II:	1-25	11.5	3.95	4.8	24	Pyridoxine	11 days
									III:	2-16	12.2	3.95	6.8	44		

* Diazine. † Amount not available. ° After 2 weeks treatment with *L. casei* factor.
I, Blood count before sulfonamide given in hospital. II, Blood count at peak of the granulocytopenia. III, Blood count after treatment with *L. casei* factor and pyridoxine. IV, Blood count made later. V, Blood count made later.

count returned to normal. The infection also cleared up. After 10 days at home the leukocyte count again fell below normal with a differential count of 50% granulocytes. He was given a second treatment at home for 2 weeks, at the end of which time the leukocyte count was fairly normal. A normal differential count has been maintained. The nurse, E. P., No. 14, had infectious hepatitis with jaundice, a condition which had been fairly frequent in this district among children. After a small dosage of sulfadiazine in the hospital, there was a further marked fall in the leukocyte count following which *L. casei* treatment was instituted. Treatment was discontinued when she returned to another hospital. Subsequently, a second affiliating nurse showed a similar neutropenia associated with infectious hepatitis but could not be treated for a sufficient period to assess the value of *L. casei* factor. Of the 11 patients who did not respond favorably, 3 children (G. S. No. 5, J. K. No. 7, and R. C. No. 6) received *L. casei* factor from 2 to 3 days only, a period of treatment too brief for lasting effect. The parents of these children, as soon as the temperature of the latter reached normal and the clinical condition appeared to be improved, insisted on taking them from the hospital. Two other children (C. H. No. 3 and C. F. No. 4), having received the drug for 6 days when they also were taken home, showed a moderate response in the leukocyte count, which might have reached normal if the treatment had been continued. There are 4 remaining patients (W. L. No. 1, G. H. No. 2, L. L. No. 9 and H. Z. No. 8) whose lowered counts were not much increased at the time of discontinuance of treatment. The first 2 of these were aged $1\frac{1}{2}$ and 2 months respectively, a period at which the bone marrow is relatively unstable. Furthermore, the concentrated liver is not well tolerated by infants and is frequently regurgitated or vomited. A persistent and intractable infection may have been responsible for the prolonged neutropenia which failed to respond to treatment in H. K. No. 8.

One of the significant items revealed by both Tables 1 and 2 is that about half of the patients already had on entering the hospital a low neutrophil count, due, we believe, as the medical histories of many of the children indicated, to previous medication with 1 of the sulfonamides, usually sulfadiazine. The lack of repair of the initial damage to the hematopoietic tissue leaves the child with a damaged bone marrow inadequate to cope with subsequent dosage of the drug. This fact is shown in Table 1 by patients J. S. No. 1, P. M. No. 3, J. M. No. 4, and M. B. No. 7, and in Table 2 by W. L. No. 1, G. H. No. 2 and J. K. No. 7 who displayed further increase in neutropenia after relatively small amounts of sulfadiazine. Here is evidence of the deleterious effect of repeated courses of the drug therapy in children. Such residual damage probably delays the achievement of good results in treatment designed to restore bone marrow to normal.

Yeast was added to the diets of some of the children receiving the dual treatment in the hope that these organisms might convert the ingested pyridoxine to a more functional form because Snell[26] has shown that yeast can effect a conversion of this enzyme into the more active compounds, pyridoxal and pyridoxamine. Conversion compounds of pyridoxine are, according to Scott *et al.*,[22] and Johnson, Hamilton and Mitchell[18] more effective in preventing deficiency anemia in chicks than the original compound. Any beneficial effect due to the yeast, if it were present, was overshadowed by the intestinal gas and abdominal distention produced by the organisms. Substitution of yeast powder for the live yeast corrected much of the distention but did not materially improve the treatment as far as we could judge. Four unlisted children, whose ages varied between 1 and 4 years, having a neutropenia associated with hypothyroidism, were given *L. casei* factor and pyridoxine for varying periods of time without any

* Diazine.
† Amount not given.
I, Blood count before sulfonamide given in hospital. II, Blood count at peak of the granulocytopenia. III, Blood count after treatment with sulfonamide given in hospital. IV, Blood count made later. V, Blood count made later.
factor and pyridoxine.

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appreciable alteration in their white blood cell count. Another child 4 years of age with a neutropenia not related to sulfonamides, the cause of which we could not determine, likewise showed little beneficial effect from the treatment with the combined enzymes.

Subsequent blood examinations have been made on several of the treated patients in an attempt to evaluate the permanency of the restitution of the damaged bone marrow by the combined treatment.

For various reasons such tests could not be made on all of the patients studied. Nine children listed in Table 1 were brought back to the hospital by their parents for later blood counts. Although the later leukocyte counts obtained on children generally showed an improvement over the neutropenia occasioned by the sulfonamide, the variation exhibited by the granulocytic values would seem to indicate a persisting instability in the myeloid elements (Table 1 and 2, IV, V). The fact that L. K. No. 13, who received a total treatment for 30 days, has maintained a high white blood cell count suggests that either the arbitrarily chosen dosage of *L. casei* factor should be greater or the duration of the treatment increased. Leukocyte counts on patients listed in Table 2 showed little change in the leukocyte count following treatment. Varying grades of damage to the bone marrow may be produced by sulfonamides. These changes range from the mild degeneration reflected in slight depression of the neutrophilic count with spontaneous return to normal on discontinuance of the sulfonamide to the extreme destruction found in aplastic anemia as shown by severe neutropenia and failure to respond to any known therapeutic agent. Obviously such variations call for widely differing periods of treatment to repair completely the damage.

It is possible that pyridoxine, the adjuvant selected by us for use with the *L. casei* factor, might advantageously be replaced by some other member of the vitamin B group. A few patients responded to *L. casei* factor alone. This observation suggests the possibility that this substance given in sufficient quantity might effect a satisfactory change in the leukopenia. At present we are testing the efficiency of a higher dosage of folic acid with a preparation kindly supplied us recently by Dr. T. H. Jukes.

Although the series of patients included in this preliminary report is not extensive and the results are less conclusive than might be desired, the results of the study are put on record in the hope that they may be of use to other workers in this field.

Summary. Of 22 children and 1 adult who had developed granulocytopenia, following sulfonamide therapy, 13 children showed a favorable response in the granulocyte count after treatment with *L. casei* factor. Pyridoxine hydrochloride was used as an adjuvant to *L. casei* factor in many of the children. White blood counts made on 9 of the 13 children at different periods of time after treatment indicated that the increase in granulocytes obtained with the *L. casei* factor was maintained in half of the children only. The low initial response as well as the subsequent variation in the level of granulocyte values is believed due to inadequate dosage of *L. casei* factor.

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VARIATIONS IN SUSCEPTIBILITY TO THERAPEUTIC MALARIA

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Individuals show a variable response in their susceptibility to therapeutic malaria. During the past year 300 members of the Army (225 whites, 75 Negroes) with various types of neurosyphilis have been treated with therapeutic malaria at this hospital. These men represent a cross-section of the population of this country. Many of them have lived or served in areas where malaria is endemic.

Of the white patients, 208 were inoculated with *Plasmodium vivax*. Of these, 185 (90%) had a satisfactory therapeutic course of 10 or more paroxysms following the primary inoculation. Of the 23 patients who failed to get an adequate febrile reaction with *P. vivax*, 14 gave a history suggestive of previous experience with malaria, 2 had spent some time in endemic malaria areas overseas, and 2 were natives of the Mediterranean Coast. Four, even after persistent questioning, were certain that they had never had malaria. One was not mentally competent. All subsequently received adequate fever from other strains and species of malaria.

Seventeen of the white patients were inoculated primarily with *Plasmodium malariæ* (*quartan*) because of a history which suggested previous experience with natural vivax malaria. All but 1, a Puerto Rican with a history of chills and fever, had satisfactory clinical responses, with adequate numbers of paroxysms and hours of fever. This Puerto Rican was reinoculated with a Southwest Pacific strain of *P. vivax* and had an excellent course.

The 75 Negroes were all inoculated primarily with *P. malariæ*. There was a satisfactory clinical response of more than 8 paroxysms, with temperature elevation over 103° F., in all but 7 of the cases. Of the 7 failures, 2 subsequently received adequate treatment with falciparum malaria and 4 of the remainder received hypertherm cabinet therapy. The last one, a case of asymptomatic neurosyphilis with conversion hysteria, refused further fever therapy.

Our studies have corroborated the generally accepted opinion that Negroes and individuals from the Mediterranean area are refractory to inoculations with *P. vivax*. We have also found that soldiers from endemic areas in Puerto Rico and the southeastern United States who have had a history of chills and fever, are usually unresponsive to inoculation with *P. vivax*. Such individuals should routinely be given primary inoculations with *P. malariæ*.

Quantitative daily parasite counts and hourly temperature records have shown that 4 types of reactions are encountered: (1) hyperimmune, (2) immune, (3) partially immune and (4) hypersusceptible.

The *hyperimmune* individual is unusual and, from a therapeutic standpoint, is practically never encountered. An inoculation of 50 to 100 million trophozoites causes neither an elevation of temperature

nor a demonstrable parasitemia. Such a person has homologous immunity, presumably having had previous experience with the same strain of malaria.

The *immune* patient, after inoculation with several million plasmodia, subsequently develops a slight parasitemia (but not up to therapeutically activating levels) which is followed by a rapid disappearance of the parasites from the blood, and is unaccompanied by any febrile response over 100° F. This reaction was frequently encountered in colored soldiers inoculated with *P. vivax*. When found in white patients it may be taken as evidence that they have had previous experience with a homologous strain of malaria.

encing 5 or less paroxysms of fever to 103° F., and (*b*) those experiencing 6 to 10 such episodes. This type of response indicates that the individual had previous experience with a heterologous strain of malaria, and seldom is the clinical course sufficient to be considered a successful treatment. A certain number of these patients will evade pre-inoculation recognition and in the interest of conservation of time and morbidity they should be promptly discovered post-inoculation. The treatment with a plasmodicidal drug and re-inoculation with another species or strain of malaria should be effected upon recognition of this immune state.

Of our 208 primary vivax inoculations

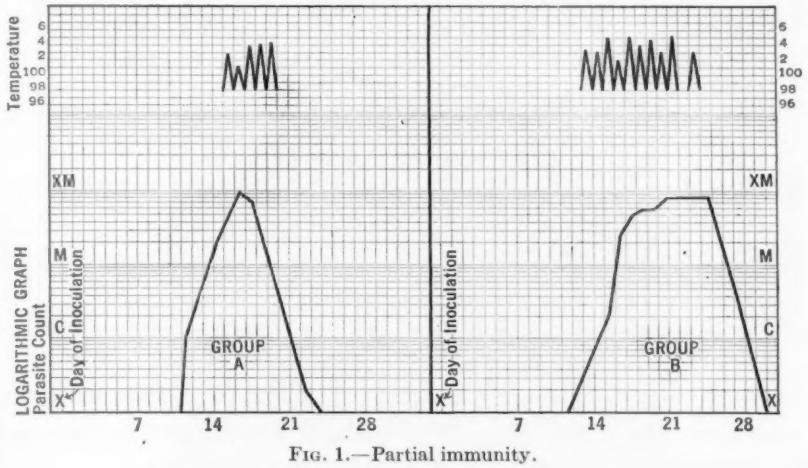

FIG. 1.—Partial immunity.

Those with *partial immunity* are a provoking problem in therapeutic malaria. Their recognition is important, and they may be discovered by eliciting a history of a previous attack of malaria before inoculating them. Parasites appear in the blood of these individuals and increase to a density of several hundred per c.mm., before any febrile response occurs. The patient experiences from 3 to 7 paroxysms of fever, whereupon the parasite count spontaneously drops precipitously and the patient becomes afebrile. Partially immune responses (Fig. 1) may be divided into 2 groups: (*a*) those experiin white soldiers, 23 exhibited a partial immune type of reaction. Nine of these, except for the fact that they were a part of a special investigative program, would have been primarily inoculated with quartan malaria because of a suspicious history of chills and fever. These were inoculated with Southwest Pacific vivax and the result of that study, which was an investigation to determine the relationship between various strains of vivax malaria, will be described in another communication.

Of the 23 cases, 15 were in Group A and were subsequently reinoculated, 5 with

heterologous strains of vivax and 10 with quartan malaria. Eight were in Group B, of which 6 were re-inoculated with heterologous vivax and 2 with quartan. All had additional paroxysms to the therapeutic optimum with the single exception of a native of Greece. This soldier, primarily inoculated with Southwest Pacific vivax, was inoculated after his immune response thereto with quartan malaria which also failed to produce a desirable therapeutic level of fever. Falciparum malaria was finally used with excellent results.

period even after the patient becomes afebrile. These patients, whom Boyd describes as having a pristine susceptibility, may go on to a prolonged number of paroxysms unless interrupted by a plasmodicidal drug. In our series, 27 paroxysms was the highest total permitted. Boyd[1] has observed continuous clinical activity without a remission for 95 days of fever. He has found that in the hypersusceptible group the number of febrile experiences averages between 16 and 25 days before a spontaneous remission occurs. This type of reaction is illustrated

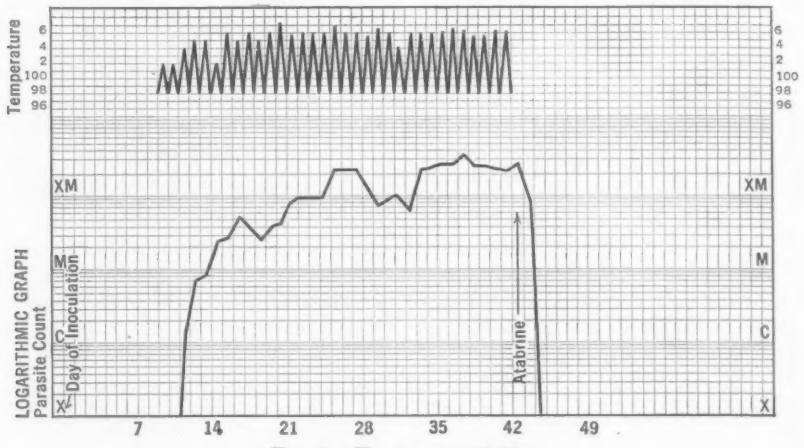

FIG. 2.—Hypersusceptibility.

Our experience has prompted us to routinely re-inoculate the patients in Group A with *P. malariæ* (*quartan*) and those in Group B with a heterologous vivax strain. This assures, with rare exceptions, a completion of a satisfactory number of paroxysms for those in Group A. The use of a heterologous vivax strain in Group B in most instances insures a sufficient added number of febrile episodes and, because of the shorter incubation period and the quotidian or tertian cycle of the paroxysms, many hospital days are saved.

The *hypersusceptible* individual usually becomes febrile several days before parasites are microscopically discernible in the blood. The parasite count rises to a high level, which is maintained for the entire

in Figure 2 and usually indicates an initial encounter with malaria.

The daily quantitative determination of the parasite count is highly desirable. It permits the early recognition of exuberant or runaway infections and encourages the prompt institution of measures designed to terminate the therapy or to bring it within bounds. It has also been employed profitably to forecast the immune types of reaction allowing us to take appropriate steps to terminate the morbidity-producing but therapeutically unsatisfactory parasitemias. Re-inoculation with a different strain or species of malaria, as previously described, may then be performed earlier than would be otherwise

possible, thus saving valuable hospital days.

Technique. The technique of the quantitative parasite count, which is Boyd's modification of that described by Earle and Perez,[2] may be described in outline form as follows:

1. Materials required:
   (*a*) Capillary pipettes graduated to deliver 5 c.mm. of blood.
   (*b*) Glass slides on which are ruled or etched rectangles measuring 3 by 15 mm.
   (*c*) Microscope, the ocular of which contains a Howard disk micrometer, the surface of which is ruled with 1 large square, divided into 16 minor squares and so calibrated that with a predetermined tube length, the area on a slide covered by the large square on the micrometer is known.
   (*d*) Diluted Giemsa's stain.

2. Methods:
   (*a*) Discharge exactly 5 c.mm. of blood on the ruled rectangle of the slide, carefully avoiding bubbles. With a needle-point carefully spread the blood out to the edges and into the corners of the ruled area. Allow to stand in a horizontal position until dry. Since 5 c.mm. of blood are spread out over 45 sq. mm., there will be spread over each sq. mm. of the rectangle 0.11 c.mm. or $\frac{1}{9}$ c.mm. of blood.
   (*b*) Stain smear in Giemsa's stain as any other thick smear, wash, drain and dry.
   (*c*) Assuming that calibration of the micrometer disk has shown that the outline of the large square covers 0.01 sq. mm. on a slide, when the stained smear is placed under the microscope it will be necessary to count the parasites observed in 100 consecutive and discrete fields to get a sample of the parasites in the blood spread over 1 sq. mm. The fields should be selected while transversing the smear on different parallel lines. The total of the parasites counted in 100 fields will, when multiplied by 9, give the number per c.mm. (Fig. 3.)

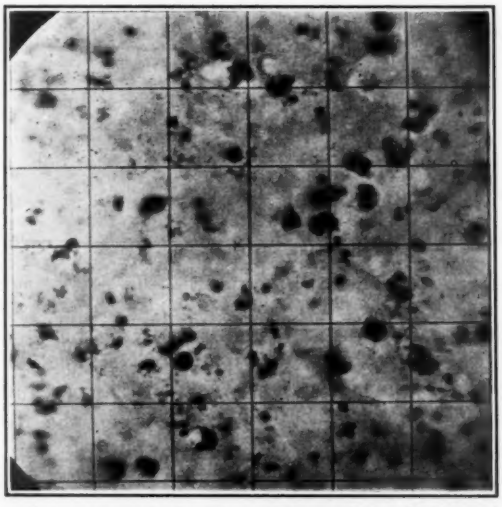

FIG. 3.—Photomicrograph (× 95) with the Howard Disc of A. Thick malaria smear (*P. vivax*). Parasite count = 42,000 per c.mm.

Vivax parasitemias usually average 20,000 to 40,000 per c.mm., and rarely exceed 50,000. Quartan parasitemias involving chiefly the aged erythrocytes, rarely reach a height of 20,000 per c.mm. There is no established limit to falciparum parasitemias, but the danger line is 100,000 to 200,000 per c.mm. If a falciparum

parasitemia reaches 500,000 per c.mm., death is almost inevitable.

The use of the daily quantitative parasite count is particularly helpful in following quartan infections. The incubation period of quartan malaria averages between 12 and 15 days. A rising parasite level gives assurance that a febrile course will ensue. A parasitemia failing to exceed 3000 per c.mm. 30 days following inoculation, and in the absence of any fever above 103° F., is fairly solid evidence that the patient has a relatively high degree of immunity and that some other form of therapy is indicated. History is of no value in forecasting an other 2 showed a low parasite count without any febrile response. This would seem to confirm the futility of using any vivax strain in the inoculation of colored people.

Falciparum malaria has been utilized by us in 3 cases as an adjunct to individuals showing immunity to both vivax and quartan. It should be used only on inescapable indications and under laboratory and clinical control that approaches the ideal. Quantitative parasite counts should be performed at least twice daily. Three-grain doses of quinine should be administered hourly as long as the temperature exceeds 104° F. or when the quantitative

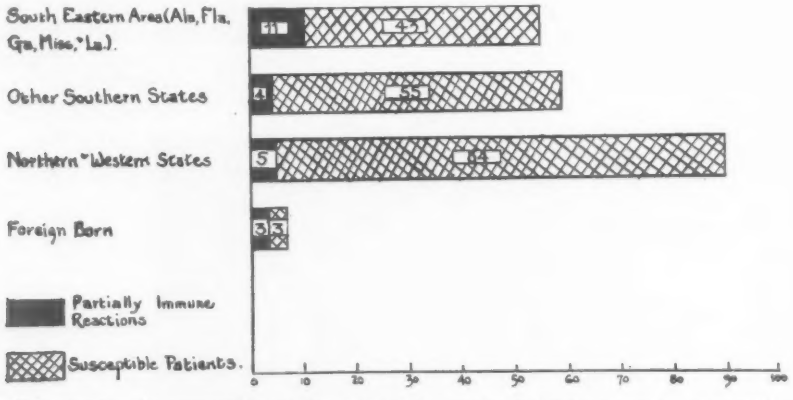

FIG. 4.—Distribution by geographic origin of 225 white patients showing number of partial immunes and susceptibles to therapeutic vivax malaria.

immune reaction in the Negro. Kroll[3] reported 11% failures in the Negroes, which parallels our experience with 7 failures out of 75 soldiers treated with quartan malaria.

An attempt was made to inoculate 8 colored patients with *P. vivax*. One was given a strain indigenous to the southern United States which resulted in a hyperimmune reaction. Seven received various strains from the Southwest Pacific, 3 by mosquito transmission and 4 by intravenous blood inoculation. Of the mosquito transmissions, 1 patient had 7 paroxysms and 2 failed to develop a parasitemia. Of the blood inoculations, 1 had 3 paroxysms, another had 4, and the parasite count is over 100,000 per c.mm. With these precautions we have been able to keep the therapy within bounds and to obtain 5 to 8 paroxysms above 103° F. before a spontaneous remission occurs.

Conclusions. 1. Three hundred members of the Army with various types of neurosyphilis were treated with therapeutic malaria. From this experience certain conclusions appear warranted.

2. Negroes should be routinely inoculated with quartan malaria.

3. Vivax malaria is a satisfactory means of inducing fever in the treatment of white patients afflicted with neurosyphilis, pro-

viding they have never had natural malaria.

4. Malaria therapists have experienced some reservations in their use of vivax in people raised in southeastern United States. Of our 43 white patients who came from this area, 80% were susceptible. Of the 11 failures, all except 1 gave a history of having chills or fever sometime during their lives. Of those from the rest of the United States, 93% were satisfactorily treated with *P. vivax* without notable geographic exceptions (See Fig. 4).

5. Candidates from the United States who give a history of a previous natural infection, those from the Mediterranean, and Puerto Rico, all should be inoculated primarily with quartan malaria.

6. White individuals who experience a spontaneous remission from a primary vivax inoculation before receiving a clinically adequate amount of fever, should be re-inoculated with quartan malaria, if they have experienced 5 or less paroxysms, or a heterologous strain of vivax if they have experienced more than 5 paroxysms.

7. Daily determinations of the parasite blood level are extremely helpful in following the course of the infection as to its severity, degree of the patient's resistance, and the early forecasting of an immune response.

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INTERFERENCE DISSOCIATION—AN EARLY FINDING IN ACUTE RHEUMATIC FEVER*

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Interference dissociation was first described in 1915 by White.[14] Dissociation of this type has been regarded as a normal finding, and as such is known merely as an expression of increased vagal tone. The condition is therefore thought to be of no particular clinical significance other than its possible confusion with heart block, which of course bears a much more serious prognosis.

During the past 2 years at our hospital we have encountered 32 cases of acute rheumatic fever, 4 of which had electrocardiographic findings of interference dissociation as an early, though transitory, finding. In 3 of these patients there was an accompanying heart block. These cases are reported in an effort to demonstrate that, although interference dissociation may in most instances be perfectly normal, at other times, it is unquestionably pathologic.

Case Reports. Case 1. A 20 year old soldier was admitted to the hospital June 2, 1943. With a history of multiple migratory joint pains. He stated that as a child he had chorea and "heart trouble," but that subsequently he successfully passed physical examinations to enter athletic sports in high school.

Examination revealed a systolic murmur at the apex and a systolic and diastolic murmur at the base of the heart. The knee joints were inflamed. Sedimentation rate was elevated. Response to salicylates was prompt.

An electrocardiogram (Fig. 1) demonstrated interference dissociation 2 days after admission. On the following day the picture was one of increasing length of the PR interval (Fig. 2) simulating Wenckenbach periods but with no dropped beats. Subsequent tracing 2 days later showed a PR interval of 0.22 second. This became normal on the following day. Patient was discharged, improved, after some 2 months hospitalization.

Diagnosis. (1) Acute rheumatic fever. (2) Valvular heart disease, mitral insufficiency, aortic insufficiency and stenosis, caused by previous attack of rheumatic fever.

Case 2. An 18 year old soldier was admitted to the hospital on May 29, 1944. He gave a history of a "cold" and sore throat 3 weeks before the onset of present symptoms. Two weeks previous to that, while home on furlough he had pneumonia, from which he made an uneventful recovery. In the past several years he has had nose bleeds on the average of about once a month. Present illness began 5 days before admission, with pain, swelling of his left knee joint, and fever. There was no history of trauma, and patient denied ever having suffered with rheumatic fever.

Examination revealed some swelling, increased warmth and tenderness on motion of the left knee joint, and a somewhat irregular cardiac rhythm. No murmurs were heard. An electrocardiogram (Fig. 3) taken 2 days after admission showed interference dissociation. This persisted for some 5 days, after which rhythm became regular.

Sedimentation rates were elevated for about a month.

Clinical course showed progressive improvement and patient was discharged after some 6 weeks.

Case 3. A 22 year old soldier was admitted to the hospital Oct. 30, 1943, and discharged Jan. 14, 1944. He gave a history of migratory joint pains, swelling and tenderness on motion for some 2 weeks before admission. Patient denied any previous similar illness.

Examination revealed some swelling, redness and tenderness of left knee joint. There were no unusual cardiac findings. An electro-

* The meaning of this special use of the term "interference dissociation" can be found under Comment on p. 690—*Ed.*

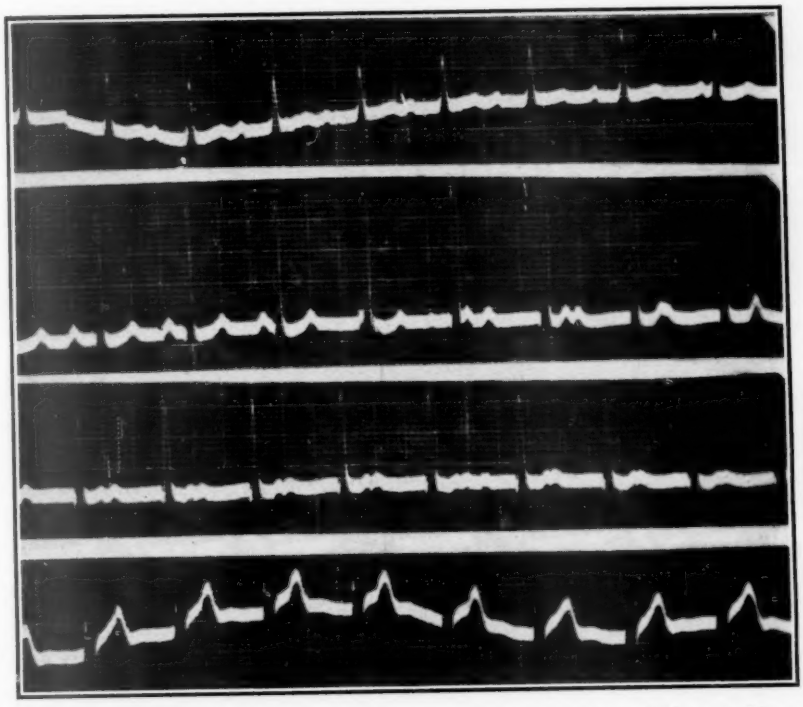

FIG. 1.—Case 1. Interference dissociation; ventricular rate 100 per minute; auricular rate 94 per minute.

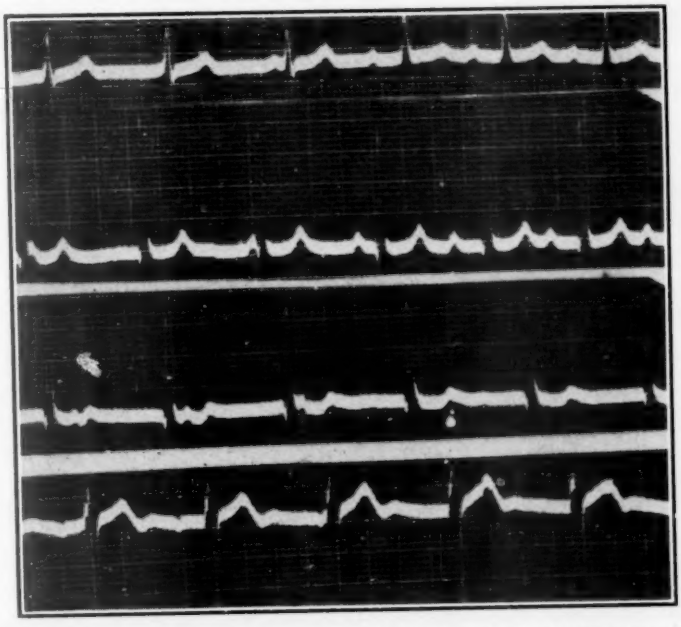

FIG. 2.—Case 1. Note in Lead 2, the increasing length of the PR intervals.

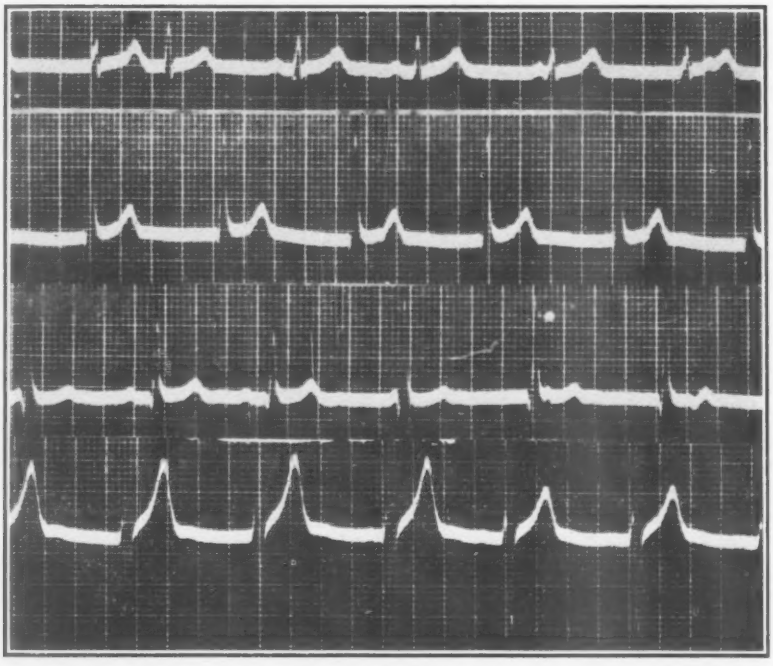

FIG. 3.—Case 2. Interference dissociation; ventricular rate 75 per minute; auricular rate 62 per minute.

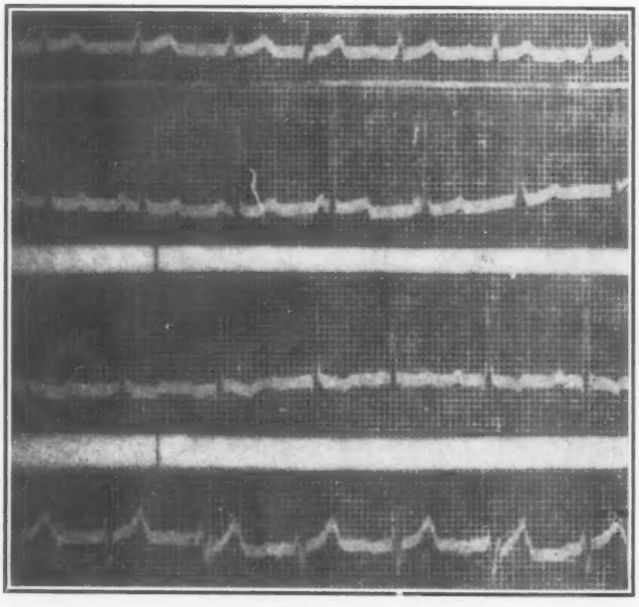

FIG. 4.—Case 3. Interference dissociation; ventricular rate 88 per minute; auricular rate 80 per minute.

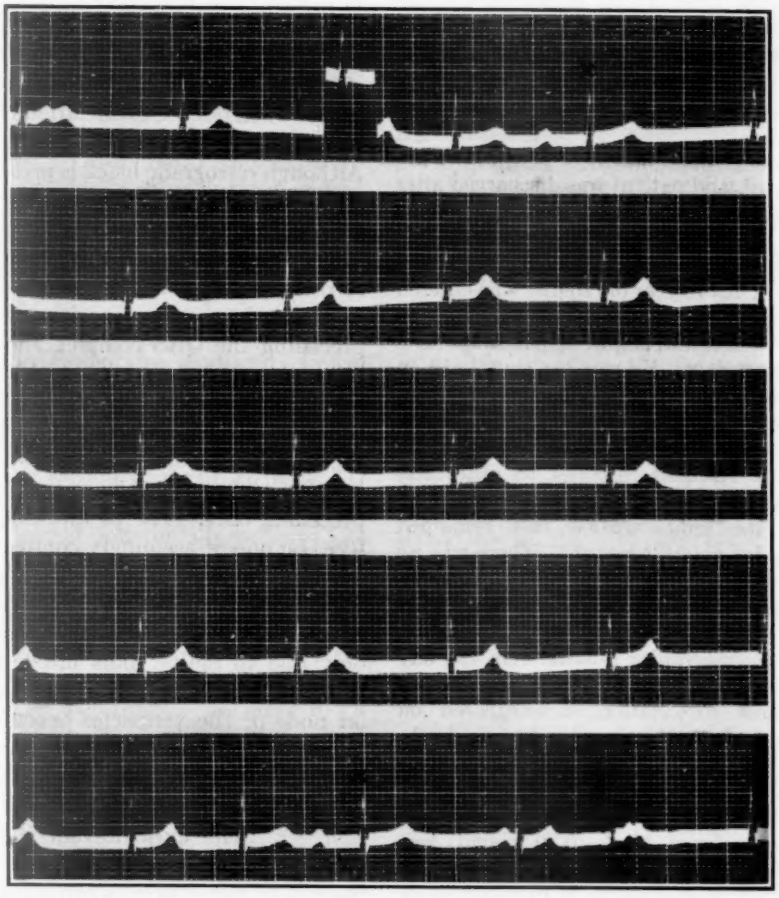

FIG. 5.—Case 4. Lead 2 taken on day after admission: shows interference dissociation and sinus arrhythmia. Several conducted beats are noted (x) with PR interval of 0.30 second.

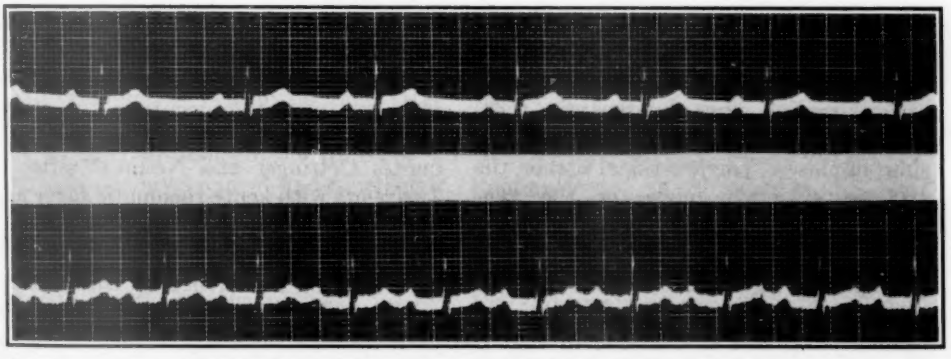

FIG. 6.—Case 4. *A*, Lead 2: shows the effect of exercise on Case 4 taken immediately after Figure 5. Dissociation has disappeared and PR interval is 0.24 second. *B*, Lead 2: following atropine sulfate gr. 1/37 subcutaneously, the dissociation disappeared. PR interval is 0.30 second. *A* and *B* demonstrate part played by the vagus in the production of interference dissociation.

cardiogram (Fig. 4) on admission demonstrated interference dissociation. These findings disappeared after 2 days. The prolongation of the PR interval endured for 5 days. Sedimentation rates remained elevated for 5 weeks.

Clinical course was one of progressive improvement, and patient was discharged after 2 months of hospitalization. At this time cardiac examination and electrocardiograms were normal.

CASE 4. An 18 year old soldier who entered the hospital on March 23, 1945 with the history of fever and migrating painful swollen joints for 6 days. He was not acutely ill on admission. The only positive findings consisted of a "hot" left knee joint and a slight irregularity to the cardiac rhythm. He showed a splendid response to salicylates and was symptom-free in a few days, although the sedimentation rate remained elevated for about 2 months. There was no evidence of valvular involvement upon discharge and Roentgen rays of the heart were normal.

Electrocardiographic Studies. On the day of admission the tracing (Fig. 5) showed interference dissociation superimposed on first degree heart block with sinus arrhythmia. This persisted for 3 days. The effect of exercise and atropine is shown in Figure 6, *A* and *B*. Dissociation was abolished and first degree heart block (0.30 second) was present. This indicated the fundamental rôle played by the vagus in dissociation of this type. Apparently the underlying picture was one of first degree heart block on which additional vagal effect produced the phenomenon of dissociation. When the latter was removed as by atropinization or through exercise, the heart block persisted.

Comment. In cases of marked sinus arrhythmia or sinus bradycardia there may be an unusually long pause between sinus impulses. The junctional tissues, the auriculo-ventricular node, or the ventricles, acting as a safety valve may take up the function of pacemaker and initiate an impulse. This is known as a nodal or ventricular escape. It is distinguished from a premature contraction in that it is not premature. A series of such beats is known as dissociation. Any sinus impulses now appearing may find the auriculo-ventricular node and ventricular musculature in a refractory state; therefore the term interference. The auricles and ventricles now beat independently of each other. Interference dissociation can therefore also be termed "double rhythm." Although retrograde block is present, sinus impulses can activate the auriculo-ventricular node and ventricles should they arrive when these tissues are no longer refractory. At this time "P" waves will be visible in the usual position and shape preceding the QRS complex and the PR interval will usually be within normal limits but may be prolonged. At this time the R wave may appear earlier or it, together with succeeding T wave, may be of a different configuration than the preceding ones. The picture may, therefore, be one of seemingly complete auriculo-ventricular dissociation interspersed with beats of sino-auricular origin.

Interference dissociation can occur not only due to faulty sinus mechanism but also at a time when the auriculo-ventricular node or the ventricles become hyperirritable. The sino-auricular node may be depressed by pressure on a hyperactive carotid sinus,[15] and by digitalis medication.[4,6,15] The auriculo-ventricular node becomes hyper-irritable and then assumes the rôle of pacemaker in infectious states[9] and following the administration of atropine[6,15] especially in its initial immediate effect.

Incidence in Rheumatic Fever.—There have appeared few reports of the presence of interference dissociation in rheumatic fever. In Dressler's[4] experience this disturbance in rhythm occurs in the course of acute articular rheumatism. Cutts quotes Oettinger and Neslin's[9] series of 7 patients with acute rheumatic fever and also report 7 cases of their own. In a footnote these authors add that they later observed the occurrence of this electrocardiographic picture in 14 out of 200 patients with rheumatic fever. Wendkos and Noll[13] studied 100 consecutive cases of acute rheumatic fever and found 6 cases of auriculo-ventricular dissociation

with associated first degree heart block. Sigler[12] illustrates a case of acute rheumatic carditis with interference dissociation. Our series of 4 cases in 32 patients with rheumatic fever seems quite representative.

Duration. This electrocardiographic phenomenon in our cases did not endure for more than 5 days. This is in accord with the experience of others,[13] although it has been known to persist for as long as 16 days.[3]

Diagnosis. The diagnosis of interference dissociation cannot be made on clinical grounds, although auscultation may reveal an irregularity of the cardiac rhythm similar to that heard with premature contractions or second grade heart block. It is only the electrocardiogram on which we can depend for the diagnosis. The confusing feature here may be the picture of heart block. The main distinction between heart block and interference dissociation is that in the latter, the ventricular rate is either equal to or greater than that of the auricles. In heart block the reverse is true.

Interference dissociation is asymptomatic. None of our patients had any complaints which might be attributed to this cardiac disturbance. It is reasonable, however, to suppose that, particularly in a hypersensitive individual, sensations as of a "skipped" beat might be complained of. Wilson[16] had 3 patients who complained of intense palpitations during experimentally induced auriculo-ventricular rhythm.

The finding of interference dissociation in our cases had no bearing on their later course. All of our patients recovered, and were at no time dangerously ill. The 1 with valvular involvement had contracted these deformities from a previous attack of this same disease. Once a doctor has ruled out complete heart block he can feel safe in offering the patient's family a good prognosis as to the early disappearance of this electrocardiographic abnormality. Wendkos and Noll[13] arrive at the same conclusion. This, however, is at variance with Cutts[3] who is in full agreement with Richardson's opinion[10] "auriculo-ventricular rhythm is not in itself fatal, but is frequently associated with severe infection or severe and chronic heart disease."

Importance. Interference dissociation has been generally considered a normal finding. Katz[7] states that it is not evidence of heart disease, and merely bears the same connotation as simple sinus arrhythmia. He considers it an expression of a "natural cardiac mechanism which comes into play to offset the consequences of marked sinus arrhythmia." However, one must doubt that this is always so. The disturbance of the cardiac rhythm, particularly as seen in our cases of rheumatic fever, associated with the well-known prolongation of the PR interval, is surely indicative of some pathologic state. It is conceivable that in certain cases of acute arthritis or fevers of undetermined origin, the finding of interference dissociation may be of aid in establishing the diagnosis.

Pathological Physiology. The basic physiological pathology may be inflammatory; that is, due to some localized myocarditis. If that is so, the transitory electrocardiographic picture may be caused by edema which is rapidly absorbed. The rôle of the vagus may be an important one. Stimulation of this nerve may be either central or peripheral. The release of the vagus by means of exercise or the administration of full doses of atropine as was performed in Case 4 indicates that at least in this instance it was a dominant factor in the production of the dissociation.

"Double rhythm" bears some analogy to the increased auriculo-ventricular conduction time. The latter is the most frequent abnormality encountered in rheumatic fever.[11] It is due to transient edema around a few small rheumatic nodules in the myocardium according to Boyd.[1] However, the vagus must play some rôle in the production of this heart block. In 2 of Wendkos and Noll's cases[13] they were able to abolish this conduction disturbance

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by the administration of 2.5 mg. atropine sulphate. Bruenn[2] obtained similar results in 19 out of 22 cases of prolonged PR interval due to rheumatic fever, by paralyzing the vagus with atropine given intravenously. He suggested that the focus of vagal irritation lay in the medulla.

Keith[8] investigated this subject in some detail. He studied a group of children with rheumatic fever, together with a control series, and he concluded that in this disease there is overstimulation of the vagus nerve resulting in prolongation of the PR interval. In his opinion the site of overstimulation of the vagus lay in its termination in the heart rather than in the medulla. As evidence for this theory of overstimulation of the vagus he describes cases of rheumatic fever with prolongation of the PR interval, which prolongation was markedly diminished by the administration of atropine in contradistinction to a control group where atropine had little effect.

In this article Keith quoted Gross and Fried[5] who designated certain local pathologic changes as the cause of the conduction time prolongations. These pathologic changes occurred in small arteries and consisted of a variety of inflammatory and vascular phenomena, including cellular infiltration of the node and surrounding tissues, edema, and destruction of collagen. Gross and Fried found exudative or vascular changes in the node and bundle tissues in approximately 66% of active cases. Keith admitted that this explanation was the most widely accepted theory, but feels that it was only applicable to the severe cases that have died of the disease, and that it did not furnish a satisfactory explanation in the mild cases referred to in his study.

Considering that in our cases of acute rheumatic fever there were found both "double rhythm" and heart block, and both of transient occurrence, it is reasonable to assume that the basic pathology in these cases of rheumatic fever is similar if not identical. In both, overactivity of the vagus nerve undoubtedly exists.

Summary and Conclusion. 1. Four cases of interference dissociation which occurred early in the course of rheumatic fever are presented.

2. A discussion of the underlying physiological-pathology is made, and a review of the literature undertaken. Interference dissociation in these cases of rheumatic fever is taken to be an expression of hyperfunction of the vagus nerve.

3. The similarity between first degree heart block and interference dissociation is pointed out. In certain questionable cases it may prove helpful in establishing a correct diagnosis, just as the finding of a prolonged PR interval is significant.

4. Although the findings of interference dissociation in rheumatic fever is a transient one, and probably bears no relation to the future outcome of the case, it must not be regarded as an expression of the natural cardiac mechanism in all cases; but in certain instances, it is of definite pathologic significance.

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CHANGES IN THE CARDIOVASCULAR SYSTEM IN SCRUB TYPHUS IN EARLY CONVALESCENCE

By Major William Likoff, M.C., A.U.S.
51st Gen'l Hospital, APO 565, San Francisco, Cal.

Because of its prevalence in areas of the Southwest Pacific and the CBI Theaters where large numbers of troops have been stationed, scrub typhus fever has become a disease of considerable importance. Its severity and mortality varies with the locality in which it is met, but in general, and for reasons not entirely understood, prolonged disability is common.

The clinical picture in a large proportion of the patients who have recovered from the disease is as characteristic as the headache, swinging temperature, rash, and eschar seen in the acute illness. These patients are profoundly weak, sleep poorly, perspire excessively, are irritable, and often have a low grade temperature elevation. When at rest the pulse rate is quite rapid, and with exercise dyspnea, palpitations, precordial pain, and syncope are common. Contrary to what might be expected, these symptoms may be out of all proportion to the severity of the acute illness.

Superficially at least the subjective complaints and clinical abnormalities which are observed during convalescence seem related to the cardiovascular system. As a consequence patients are often hospitalized with a diagnosis of chronic myocarditis or myocardial insufficiency the result of scrub typhus. On those occasions when a murmur is heard physicians have attributed valvular damage to the rickettsial infection. Finally, and in complete contrast, instances have been observed where the persistent tachycardia and poor tolerance for exercise have been attributed to an anxiety state entirely independent of any organic ailment.

This apparent confusion in the minds of physicians who have contacted patients recently recovered from scrub typhus fever emphasizes the need of an evaluation of the potential and actual cardiovascular sequelæ of the disease. Is scrub typhus unusual in its involvement of the endocardium or the myocardium? If so, how much impairment of cardiac function is to be expected? If the heart is not involved, what is the basis of the tachycardia at rest, the inability to tolerate exercise without dyspnea, and, in some instances, the actual precordial pain? A proper answer to these questions not only clarifies the problem of therapy, but will prevent a patient from unjustifiably being labeled a cardiac cripple through the misuse of such terms as myocarditis, or valvular disease.

Accordingly, an attempt was made in this study to establish the type and extent of cardiovascular dysfunction in a representative group of patients who had recently recovered from scrub typhus fever.

Material. One hundred patients, ranging in age from 19 to 35 years, were examined on the average of 49 days after the onset of the acute illness. The study included an analysis of the subjective symptoms, a physical examination, an exercise tolerance test in a limited number of instances, and at least 1 electrocardiogram on each patient.

The group was a fair cross-section of a larger one that had contracted the disease in a Southwest Pacific base where the mortality was low. With few exceptions the men were not seen during the acute illness, but only after they were well enough to have been evacuated from the forward area. Nevertheless, it was evident that few had had a particularly stormy course. This is best illustrated by the fact none had been in coma, only 1 had been given oxygen therapy, and the total febrile period for the group averaged

9 days, or roughly 5 days less than is normally expected.

The diagnosis of scrub typhus was based upon the intractable headache, remitting temperature, rash, eschar, and positive agglutination for Proteus OXK in titers of 1:160 or higher. All of these diagnostic features were not present in each case. The absence of an eschar, for example, or a negative agglutination was not considered sufficient evidence to negate the diagnosis since either or both findings may be lacking when the clinical picture is so characteristic as to be unmistakable. It is possible that some of the patients with negative agglutinations may have shown a positive test at a later date for this is known to happen as late as two months after the initial infection. Under the circumstances of this study, however, it was not possible to check the test indefinitely. Selection of the patients was such that only 6 did not have either an eschar, or a positive agglutination.

Each of the patients was interviewed by the same examiner who recorded the outstanding complaints, tabulated an average of the daily pulse rate and blood pressure, and performed the physical examination. With 1 exception, each patient had been ambulatory for at least 14 days before he was examined. In many instances repeated interviews were necessary.

In all cases at least 1 electrocardiogram was obtained with the patient at rest, and where important abnormalities were observed tracings were repeatedly taken as long as the individual was under observation.

A two-step exercise tolerance test was taken by 25 of the group. The technique was essentially that outlined by Master.[3]

Results. Complaints related to the cardiovascular system were noted in 30% of the group. In 21 of these patients the outstanding symptom was a rapid heart beat even when at complete rest. Dyspnea and precordial pain with effort was a common secondary ailment. Of the 9 who made no mention of a rapid pulse, 4 were dyspneic on effort, 3 had precordial pain and syncope, and 2 were troubled with palpitations.

The average daily pulse rates for these patients was 107, and in but 2 instances was the rate below 100. Of the 70 who either felt well or did not complain of cardiovascular symptoms only 4 were found to have a daily pulse rate that averaged over 100.

It is apparent, then, that in 70% of those in whom cardiovascular disease was suspected tachycardia was an important complaint and could be objectively proven in practically all instances, while in the others it was infrequently noted.

No important abnormalities in blood pressure were seen in any of the patients, readings ranging from 104 to 138 mm. Hg systolic, and from 60 to 90 diastolic.

The precordial pain mentioned by many as occurring during effort was piercing in character, transient, not transmitted, almost invariably localized over the left nipple, and usually aggravated by taking a deep breath. Although it is not possible to state what factors are responsible for this pain there was only a superficial similarity to angina pectoris in the several patients observed during an attack.

The 25 who took the exercise test were a mixed group of symptomatic and asymptomatic patients. In 12 the pulse rate did not return to within 10 beats of the resting level at the end of 2 minutes. All but 1 of these had so-called cardiovascular symptoms, and in 6 of those the blood pressure also failed to return to normal levels.

During the exercise tolerance test a considerable number complained of dyspnea, but in no instance was this associated with any marked degree of cyanosis, and the lungs were clear on auscultation.

On auscultation a murmur was heard in 6 of the symptomatic group and in 2 patients who had no complaints. All the bruits were systolic. The point of maximum intensity of 6 of the murmurs was at the pulmonic area, while the remaining 2 were heard best at the mitral area. In

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only 1 case was the murmur of a greater intensity than Grade 2 and this patient had a definite mitral lesion the result of rheumatic fever. A diastolic murmur was not heard in any of the patients.

Evidence of cardiac failure, such as hepatomegaly, peripheral edema, and pulmonary congestion was not found; in only 1 instance was an abnormal rhythm, other than sinus arrhythmia, detected, and this was caused by an occasional auricular ectopic beat.

a second degree heart block was critically ill, and had been given an unknown quantity of digitalis in the forward area. One week later, when normal auriculoventricular conduction had been restored, the T waves in leads 2 and 3 were sharply inverted, but not suggestive of a digitalis effect. With complete recovery the tracing was normal.

The remaining patients, including the 3 with delayed ventricular conduction, and 1 each with negative T waves in leads 2

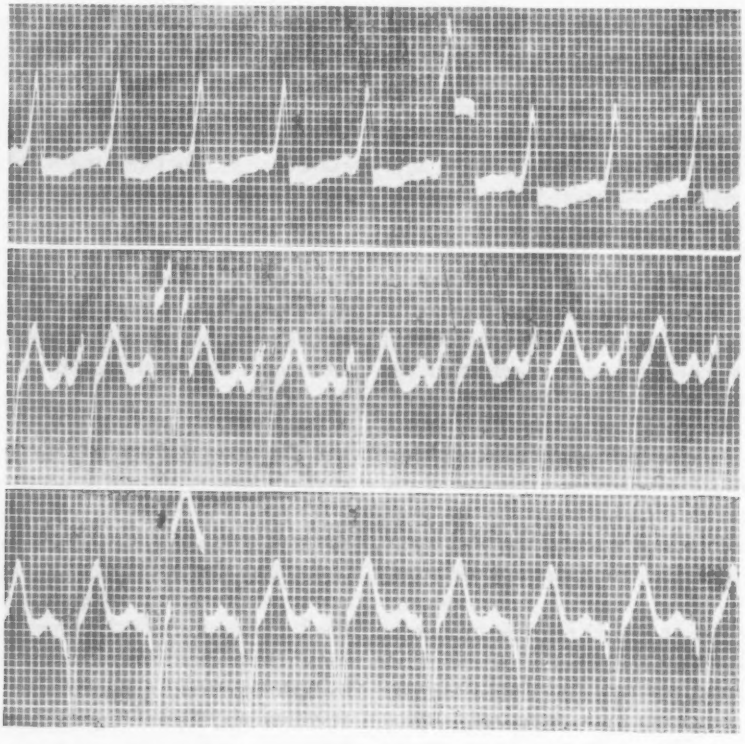

FIG. 1.—Left bundle branch block in a patient 22 years of age 43 days after the onset of scrub typhus fever.

Electrocardiographic abnormalities were detected in 10 patients all of whom were in the symptomatic group. Variations from the normal included: bundle branch block, 2; intraventricular block, 1; negative T waves in 2 or more leads, 3; splintering of the QRS without increase in duration, 3; and second degree heart block, 1.

In 5 instances the changes were transient. When first seen, the patient with

and 3, and marked slurring and splintering of the QRS in lead 2 without prolonged conduction time, continued to show such abnormalities at the time this study was concluded. None had been taking digitalis or allied drugs, and the last electrocardiogram was obtained on the average of 47 days after the onset of the illness.

Figures 1 to 4 are examples of the

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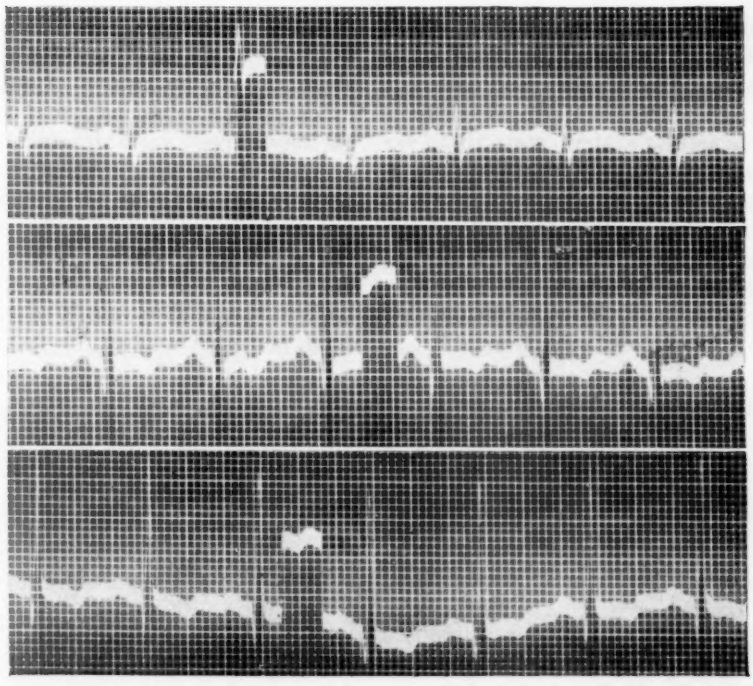

FIG. 2.—Negative T_2 and T_3, in addition to Q_2 and Q_3 in a patient 24 years of age 48 days after onset of scrub typhus fever.

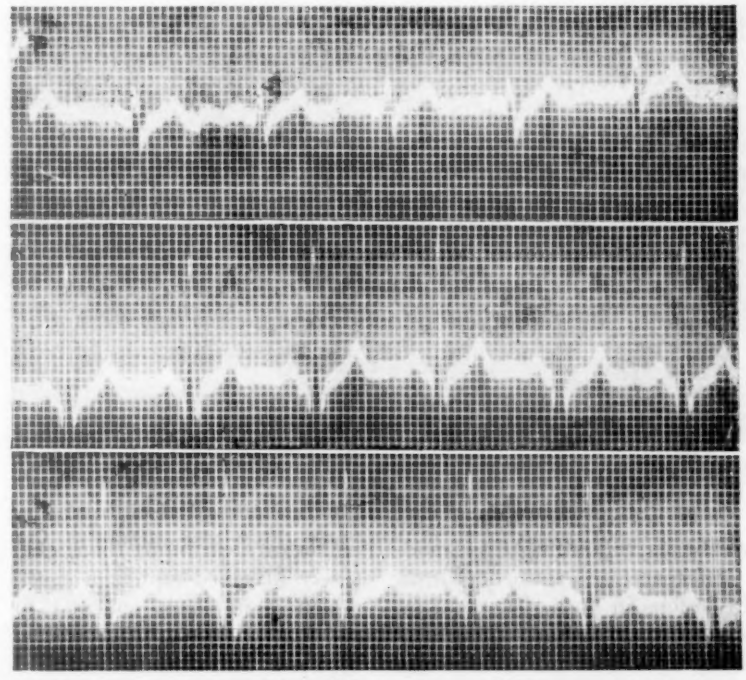

FIG. 3.—QRS duration of 0.11 second in addition to depressed ST segments in Leads 2 and 3 in a patient 21 years of age 47 days after the onset of scrub typhus fever.

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electrocardiographic abnormalities which persisted.

Discussion. Woodward and Bland,[4] discussing the effects of typhus fever upon the cardiovascular system, state that "no serious disturbance of cardiac function *per se* appeared to be responsible for the circulatory phenomenon—and transient electrocardiographic abnormalities were probably comparable to similar findings in patients seriously ill with pneumonia, and with typhoid, and with uremia."

lungs, and skin are most frequently involved. About the area of perivasculitis there may be an accumulation of monocytes, plasma cells, and lymphocytes. In the more severe cases, fragmentation and necrosis of the muscle fibers of the heart may be seen, and the edematous interstitial tissue is studded with the infiltrating cells. At least some of the myocardial degeneration may be due to the thrombosis of the smaller vessels caused by the endo- and perivasculitis.

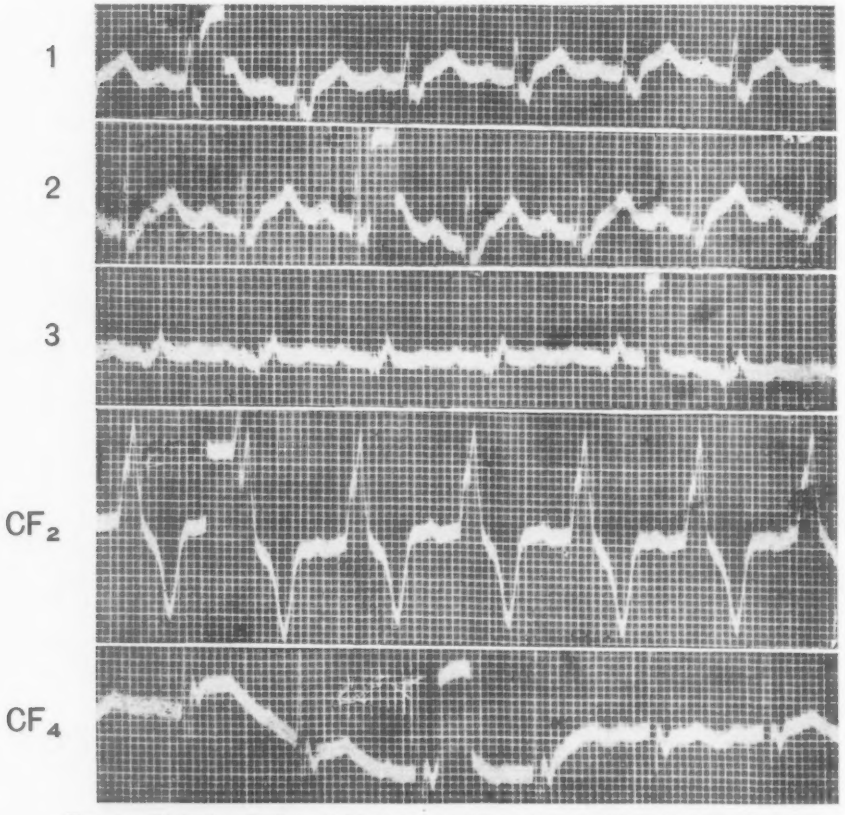

FIG. 4.—Right bundle branch block in a patient 27 years of age 46 days after the onset of scrub typhus fever.

Although the above statement was made in direct reference to acute epidemic typhus, the lesions in both rickettsial infections is somewhat similar. This consists primarily of a perivasculitis of the smaller blood-vessels. The heart, brain,

The myocardium, then, can be extensively involved and in a specific manner which is in sharp contrast to the nonspecific changes following pneumonia, typhoid, and similar severe infections. When such changes are sufficiently diffuse,

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or by chance involve areas of the heart particularly essential to normal function, such as the conduction system, the disease may not be without serious consequences.

For the period of time included in this study it is possible to draw only limited conclusions. As would be expected from the pathology of the disease, scrub typhus does not cause valvular damage. At least this was found to be the case two months after the initial infection. Examination of a considerably larger group than is included in this report further bears out that contention. When murmurs are heard, they are of low intensity, always systolic, more often heard at the base than at the apex, and are probably related to an increase in blood velocity incidental to the tachycardia with which they are usually associated.[2]

Although a considerable proportion of the patients claimed symptoms that seemed to indict the cardiovascular system, certain of those complaints, most notably precordial pain and syncope, were probably independent of any true cardiac disability. Furthermore, aside from tachycardia, it is apparent that the physical examination in the symptomatic group was negative. As an indication of organic heart disease, too much reliance cannot be placed upon the failure of the pulse or blood pressure to return to resting levels 2 minutes after a two-step exercise test. Similar results have been noted in constitutional states such as neurocirculatory asthenia.[3]

It appears that the type and extent of myocardial involvement following scrub typhus is best appreciated through a study of electrocardiographic abnormalities. Certain of the changes, such as delay in auriculoventricular conduction, negative T waves, and QRS slurring may be transient, although occasionally they may persist for a considerable time after the initial infection. Although those instances of intraventricular conduction defects represent either widespread myocardial involvement or an unfortunate localization of a more discrete lesion, further study may prove that even such significant changes may be of a transient nature as is the case following other types of acute infection.

In this study the abnormal electrocardiograms were obtained from individuals in the symptomatic group, but at the same time it was impossible to predict from subjective complaints alone which of these patients would show such changes. This may be explained on the theoretical basis that many with normal electrocardiograms had cardiac lesions so located as not to distort the heart's electrical pattern. It is more probable that these patients did not have any heart disease, and their complaints were more closely related to the asthenic state which followed the long febrile and toxic illness. Nevertheless, it is of particular importance that in this study 1 in 3 of the individuals with either tachycardia, dyspnea, precordial pain, or syncope did show an abnormal electrocardiogram, and 1 in 10 had considerable involvement of the intraventricular conduction system. Finally, abnormalities were not seen where there were no symptoms.

A better understanding of scrub typhus fever should follow the realization that the disease may result in myocardial injury. Within limits, an estimation of these effects and a better defined prognosis may be obtained by means of an electrocardiogram during the acute and recovery stages. Of equal importance is the fact that the so-called cardiovascular symptoms occur when heart disease cannot be demonstrated. In such instances, and until a longer follow-up study answers the problem more completely, the use of the terms chronic myocarditis or myocardial insufficiency is an unwise presumption.

Summary and Conclusions. 1. A study was made of 100 patients on the average of 49 days after the onset of scrub typhus fever. It included an analysis of the subjective symptoms, physical examination, a limited number of exercise toler-

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ance tests, and at least 1 electrocardiogram on each patient.

2. Symptoms which were apparently related to a dysfunction of the cardiovascular system and which included tachycardia at rest, dyspnea and precordial pain following exercise, and syncope were found in 30% of the patients.

3. No evidence of cardiac failure or organic valvular disease was noted in any of the patients; but tachycardia was an actual finding in practically all of the symptomatic group, whereas in the others it was infrequently observed.

4. Of 12 patients showing an abnormal response to the two-step exercise test, 11 were in the symptomatic group; but this test was thought to be inconclusive evidence of organic heart disease.

5. Ten patients showed abnormal electrocardiograms and each of these was in the symptomatic group. In 5, where there was either delayed auriculoventricular conduction, negative T waves in 2 or more leads, or slurring of the QRS complex without prolonged duration, the changes were transient.

6. The most significant electrocardiographic changes were observed in 3 patients who had either bundle branch or intraventricular block, which persisted over the period included in this study.

7. No explanation can be made as to the cause of symptoms relative to the cardiovascular system in those cases where there was no objective evidence of heart disease.

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AN 18-HOUR CONCENTRATION TEST OF KIDNEY FUNCTION

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A simplified concentration test of renal function has been used at this University Hospital and has been found satisfactory for clinical use. It is based on the principles of the 38 hour concentration test of Lashmet and Newburgh,[2] which imposes a maximal strain on the kidneys in order to secure the most concentrated urine specimen possible. The new test is performed over a period of only 18 hours and does not require the use of special diet. It entails little hardship for the subject and is particularly convenient for use on ambulatory patients.

Procedure. The test is carried out by having the subject finish his usual supper by 6 P.M. He then has nothing to eat or drink until noon the following day; he may carry on ordinary activity during this time. Urine specimens are collected at 8 A.M., 10 A.M., and 12 NOON, with complete emptying of the bladder each time. The specific gravity of each specimen is then determined, with the urine at room temperature and with an ordinary urinometer which has been checked with distilled water.

The most concentrated specimen is tested for the presence of protein, and if present its amount is quantitatively determined in order to correct the specific gravity when necessary. For every 1% of protein present in the urine, 0.003 is subtracted from the observed specific gravity; any proteinuria less than 0.3% does not need to be considered. Thus the specific gravity of most urines will not require correction.

We have further simplified the easy and accurate method of Lashmet and Newburgh[3] for quantitative measurement of proteinuria:

*Method.** To 1 cc. of urine add 9 cc. of distilled water, making a 1:10 dilution. Add the diluted urine to the U mark of Tube 1 and then add 2% sulfosalicylic acid up to the R mark. Mix thoroughly, and allow to stand for 3 minutes. If the resulting turbidity matches that of the *standard tube*, the urine contains 0.3% protein; the specific gravity of the urine is then corrected by subtracting 0.001. If the turbidity is less than that of the standard tube, no correction of the observed specific gravity is necessary.

If the turbidity of Tube 1 is greater than that of the standard tube, add the 1:10 diluted urine to the U mark of Tube 2, and then add 2% sulfosalicylic acid to the R mark. Mix thoroughly and allow to stand; if the turbidity matches that of the standard tube, the urine contains 0.6% protein. The observed specific gravity then is corrected by subtracting 0.002. If the turbidity is greater than that of the standard, add the diluted urine to the U mark of Tube 3, and sulfosalicylic acid to the R mark. If the turbidity resulting in Tube 3 matches that of the standard tube, the urine contains 1% protein. The observed specific gravity is then corrected by subtracting 0.003. Urine containing more than 1% protein should be diluted 1:20, and the foregoing procedure with the 3 tubes is repeated.

The 2% sulfosalicylic acid reagent may turn pink on standing. Such solutions should be discarded, for the pink cast interferes in accurate comparison with the standard.

Preparation of the standard turbidity suspension: A stock suspension is first prepared. To 200 cc. of distilled water in a 500 cc. volumetric flask, add 50 cc. of 0.1 normal

* A set of calibrated tubes, standard tube, and a support (A21-195) may be obtained from Eberbach & Son, Co., Ann Arbor, Mich.

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sodium hydroxide solution and 8 gm. of copper sulfate (hydrous). Then add distilled water to 500 cc. Shake the stock suspension vigorously to insure uniform turbidity. Exactly 2 cc. of this mixture is transferred by pipette to a test-tube, and 23 cc. of distilled water is added. This is the standard tube, and it can be made permanent by drawing out its open end and sealing in a flame. Before using, the standard tube should be inverted several times to obtain uniform turbidity.

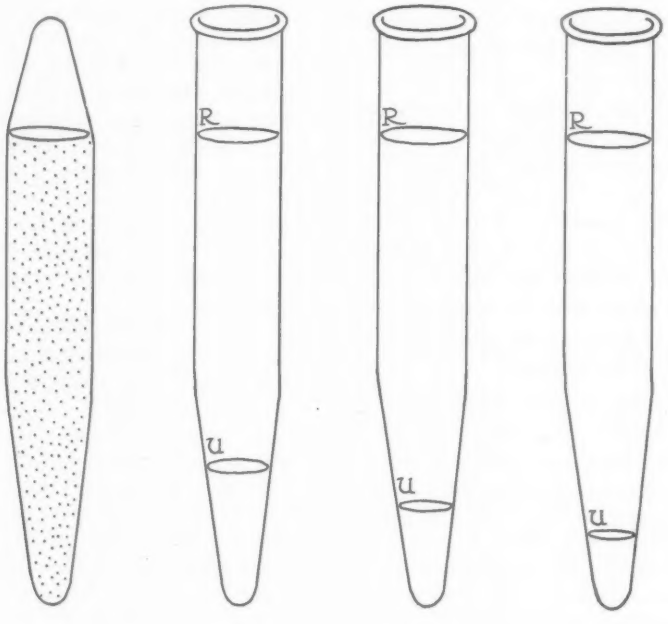

FIG. 1.—Set of tubes for rapid quantitative determination of proteinuria.

Tube 1:
U mark is at 1.66 cc. = 0.3% protein.
Tube 2:
U mark is at 0.83 cc. = 0.6% protein.
Tube 3:
U mark is at 0.5 cc. = 1.0% protein.
The R mark is at 12.5 cc.

Results. This test was performed on 40 normal medical students who showed no evidence of renal disease. The urinalysis on each subject was entirely negative. Of the subjects, 38 concentrated to a maximum specific gravity of 1.025 or higher, and 2 subjects concentrated to 1.024. We thus have placed a maximum specific gravity of 1.025 as the lower limit of normal for this 18 hour renal concentration test.

A single determination was done on each of the 40 normals except 1. The latter concentrated only to a specific gravity of 1.020 on his first determination, but on his second test the maximum specific gravity was 1.025. It is thus recommended that a single low determination not be accepted as evidence of impaired renal function, and that the test be repeated before such a conclusion is reached.

It is realized that normal kidneys may concentrate to a higher specific gravity when the test is carried out over a longer period of time. The value of 1.029 is the lower limit of normal for the 38 hour concentration test of Lashmet and Newburgh. But it is felt that by the end of 18 hours

TABLE 1.—THE MAXIMUM SPECIFIC GRAVITY OF 40 NORMAL SUBJECTS

Maximum specific gravity	No. subjects	Maximum specific gravity	No. subjects
1.024	2	1.030	4
1.025	6	1.031	4
1.026	8	1.032	3
1.027	4	1.035	1
1.028	4	1.040	1
1.029	3		

TABLE 2.—INTERPRETATION OF MAXIMUM SPECIFIC GRAVITY VALUES IN THE 38 HOUR AND 18 HOUR CONCENTRATION TESTS

Kidney function	Maximum specific gravity	
	38 hour test	18 hour test
Normal	1.029 and higher	1.025 and higher
Borderline	1.027–1.028	1.024
Slight impairment	1.022–1.026	1.020–1.023
Moderate impairment	1.016–1.021	1.015–1.019
Marked impairment	1.015 and below	1.014 and below

TABLE 3.—COMPARISON OF RESULTS OF 38 HOUR AND 18 HOUR CONCENTRATION TESTS IN 100 PATIENTS WITH HYPERTENSIVE DISEASE (FAILURE OF CORRELATION IN 11 CASES)

Case No.	38 hr. test	18 hr. test	Correlation	Case No.	38 hr. test	18 hr. test	Correlation
1	1.023	1.021	+	51	1.030	1.024	+
2	1.027	1.024	+	52	1.025	1.025	+
3	1.030	1.024	+	53	1.031	1.026	+
4	1.028	1.026	+	54	1.025	1.016	0
5	1.028	1.024	+	55	1.025	1.023	+
6	1.018	1.014	0	56	1.029	1.026	+
7	1.033	1.029	+	57	1.030	1.017	0
8	1.028	1.024	+	58	1.028	1.025	+
9	1.021	1.017	+	59	1.024	1.025	+
10	1.024	1.022	+	60	1.026	1.027	+
11	1.016	1.013	+	61	1.024	1.022	+
12	1.015	1.014	+	62	1.025	1.023	+
13	1.010	1.013	+	63	1.028	1.026	+
14	1.023	1.019	0	64	1.021	1.026	+
15	1.028	1.026	+	65	1.029	1.024	+
16	1.021	1.020	+	66	1.028	1.017	0
17	1.022	1.020	+	67	1.026	1.023	+
18	1.023	1.020	+	68	1.030	1.028	+
19	1.026	1.024	+	69	1.031	1.028	+
20	1.026	1.023	+	70	1.026	1.022	+
21	1.020	1.018	+	71	1.024	1.020	+
22	1.027	1.024	+	72	1.023	1.022	+
23	1.024	1.023	+	73	1.027	1.024	+
24	1.029	1.024	+	74	1.028	1.012	0
25	1.032	1.031	+	75	1.026	1.021	+
26	1.031	1.025	+	76	1.023	1.026	+
27	1.024	1.018	0	77	1.024	1.025	+
28	1.025	1.020	+	78	1.022	1.020	+
29	1.032	1.020	0	79	1.029	1.024	+
30	1.030	1.027	+	80	1.025	1.021	+
31	1.028	1.024	+	81	1.024	1.025	+
32	1.022	1.021	+	82	1.029	1.027	+
33	1.025	1.023	+	83	1.029	1.020	0
34	1.028	1.025	+	84	1.028	1.024	+
35	1.028	1.025	+	85	1.023	1.022	+
36	1.028	1.024	+	86	1.031	1.026	+
37	1.024	1.022	+	87	1.028	1.027	+
38	1.026	1.027	+	88	1.024	1.023	+
39	1.024	1.020	+	89	1.027	1.026	+
40	1.028	1.024	+	90	1.022	1.023	+
41	1.028	1.026	+	91	1.017	1.025	+
42	1.026	1.023	+	92	1.032	1.031	+
43	1.026	1.024	+	93	1.019	1.017	+
44	1.026	1.027	+	94	1.025	1.020	+
45	1.015	1.012	+	95	1.012	1.012	+
46	1.024	1.020	+	96	1.025	1.021	+
47	1.034	1.026	+	97	1.030	1.024	+
48	1.032	1.020	0	98	1.028	1.026	+
49	1.032	1.027	+	99	1.026	1.015	0
50	1.029	1.025	+	100	1.027	1.025	+

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the kidneys have been subjected to a strain sufficient to enable an adequate differentiation of the normal from the abnormal.

In order to determine whether the 18 hour test is as effective a measure of kidney function as the 38 hour test, a comparison of results was made in 100 cases of hypertensive disease on whom both the 38 hour and the 18 hour tests had been performed. The shorter test was done when these patients returned 1 year later for studies. There was failure of correlation of the results in only 11 of the 100 cases; thus the 18 hour test is sufficiently accurate to warrant its use. The disparity of the results of the 2 tests in these 11 cases may be partly accounted for by the possible increase of impairment of kidney function occurring during the year intervening between the 2 tests, for each of these patients had hypertensive disease. Also, only a single determination was done in each case even when the result was abnormal.

Of 200 cases of essential hypertension, 124 cases (62%) showed impaired concentrating ability.[1] Each of these patients had hypertensive disease of sufficient severity to warrant hospitalization for surgical treatment of the hypertension; the elevated blood pressure was not a coincidental finding. The concentration test was found to be more sensitive than the urea clearance test in detecting early kidney damage in essential hypertension. It was also found that it is unnecessary to measure the urea clearance when the concentrating ability is normal.

Each of 8 cases of glomerulonephritis, both subacute and chronic, showed impaired concentrating ability. The maximum specific gravity in these cases ranged from 1.010 to 1.020.

Summary. An 18 hour concentration test of kidney function is presented. It is easily performed, and it is particularly suitable for use on ambulatory patients. Under the conditions of this test, normal kidneys concentrate urine to a specific gravity of 1.025 and higher, while diseased kidneys do not.

A simple, rapid, and accurate method for quantitative determination of proteinuria is also presented. It is based on the comparison of the turbidity of urine in which protein has been precipitated by 2% sulfosalicylic acid, with the turbidity of a permanent, standard suspension of inorganic substance.

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THE RELATIONSHIP BETWEEN PACKED RED CELL VOLUMES AND LYMPHOCYTE COUNTS

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A relationship between cell pack (hematocrit) values and the percentage of lymphocytes found in the differential count has recently been demonstrated by Jung, Hepler and Maynard.[1] In the course of blood investigations on 35 students they noticed that subjects with low cell pack volumes tended to have high lymphocyte percentages and *vice versa*. Hematologic data from 160 dispensary patients disclosed the same relationship, especially in those patients with cell pack volumes above 38 cc. per 100 cc. of blood. Jung, Hepler and Maynard[1] think that their finding may be evidence of a reciprocal relationship between lymphocyte production and erythrocyte production, or alternatively that it may be due to periodic increases in the discharge of lymph from the thoracic duct into the veins, so that from time to time in the normal body there is hemodilution accompanied by a release of lymphocytes into the blood stream.

However, these changes in lymphocyte percentage do not necessarily indicate that the number of lymphocytes per c.mm. of blood has altered: the percentage of lymphocytes in the differential count may be high because there are many lymphocytes in circulation or because there are few granulocytes. It may well be that the reciprocal relationship between lymphocyte percentage and cell pack volume found by Jung, Hepler and Maynard[1] is really due to changes occurring in the granulocytes at different cell pack values. The point can readily be settled by finding the absolute number of granulocytes and lymphocytes per c.mm. which correspond to different cell pack volumes; if there is any true relationship between cell pack volume and lymphocyte production or release, then it should still be demonstrable in the absolute lymphocyte count.* We have examined 100 subjects with this point in view.

Material and Methods. *Subjects.* One hundred males with cell pack volumes above 38 cc. per 100 cc. of blood (the range in which the association with lymphocyte percentage is most evident[1]) were used. They were either healthy people or had some local lesion which would be unlikely to affect the blood picture (non-syphilitic mental observation cases, and so forth). Their ages ranged from 16 to 61 years.

Blood Samples. These were collected between 7.30 and 10 A.M. with the subject fasting. Five cc. of blood were taken by venepuncture with the minimum of venous stasis and transferred to a tube containing a suitable quantity of Wintrobe's[2] oxalate mixture. This venous sample was used for cell pack determination, white cell count and differential count.

Cell Pack Determination. The blood was spun in Wintrobe tubes for 30 minutes in an International centrifuge (head No. 240) at 3000 revolutions per minute; the speed was checked by tachometer.

White Cell Count. Dilutions were made using 5 cc. of white cell fluid and 0.2 cc. of

* We believe that the authors' point is well taken; absolute numbers are usually of more value than percentages. However, it should be realized in this case that the direct estimations are of the total numbers of leukocytes and percentages. The absolute values, being computed from the two figures, each of which may have considerable range of error, might be even further from actuality.—Editors.

blood; 9 fields of 1 sq. mm. each were counted in the hemacytometer chamber.

Differential Count. Immediately after removing the venous sample, coverslip films were made from a fixed quantity of blood. The films were stained by Leishman's stain and 300 cells were differentiated by an observer who was unaware of the other data in the investigation. Smear cells and degenerate forms were found to be distributed without relation to the cell pack volume and were ignored in the calculation of the differential count.

TABLE 1.—RELATION OF GRANULOCYTES AND LYMPHOCYTES TO CELL PACK VOLUME

Cell pack volumes (cc. per 100 cc. blood)	No. in group	Total leukocytes (per c.mm.)	Granulocytes		Lymphocytes	
			%	Per c.mm.	%	Per c.mm.
39–44.5	25	7148	63.26	4610	33.28	2305
45–47.5	49	7570	65.26	4934	30.59	2320
48–56.5	26	9390	68.12	6422	27.98	2549

TABLE 2.—CORRELATION COEFFICIENTS

Hematocrit value and total leukocytes per c.mm.	=	$+0.319 \pm 0.090$*
Hematocrit value and granulocytes, %	=	$+0.271 \pm 0.093$*
Hematocrit value and granulocytes per c.mm.	=	$+0.347 \pm 0.088$*
Hematocrit value and lymphocytes, %	=	-0.242 ± 0.094*
Hematocrit value and lymphocytes per c.mm.	=	$+0.062 \pm 0.100$

The regression lines do not differ significantly from linearity.
* Statistically significant association.

Results. Table 1 shows the general relationships. As the cell pack volume rises, the total white cell count per c.mm. increases. This is almost entirely due to an increase in the number of granulocytes per c.mm.; the percentage of granulocytes is consequently increased and the percentage of lymphocytes reduced. There is no significant change in the number of lymphocytes per c.mm. at different cell pack levels. Table 2 indicates that this interpretation of the results is statistically sound.

Thus, the relationship between cell pack volumes and lymphocyte percentages does not indicate any real change in the number of lymphocytes in circulation, but is due to an increase in the number of granulocytes in circulation as the cell pack volume rises. Presumably the well-known diminution of granulocytes in many types of anemia and their increase in polycythemia vera are extreme instances of this association between the number of granulocytes and erythrocytes in circulation.

Summary. The negative correlation between cell pack volumes and lymphocyte percentages has been confirmed. This effect is secondary to changes occurring in the percentage and absolute count of granulocytes. There is no significant change in the absolute lymphocyte count at different cell pack levels within the range studied.

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THE SEDIMENTATION RATE AS AN AID IN THE DIAGNOSIS OF ACUTE POLIOMYELITIS

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From July to November 1945, there have been 223 cases of poliomyelitis interned at the South View Hospital of the Milwaukee Health Department. During that time more than 100 cases have been sent to the Hospital as suspected poliomyelitis. During this 4 month period we have had 420 consultation calls in the city. Frank cases of this disease were diagnosed quite readily, by the attending physicians. However, the borderline cases and the abortive types caused considerable difficulty in diagnosis. This necessarily meant that the suspected poliomyelitis case was sent to the hospital for a spinal fluid examination and observation. Attending physicians occasionally are hesitant in sponsoring a spinal puncture as family objections may provoke delay in carrying out this laboratory aid. There is still a small amount of skepticism on the part of the laity to subscribe to spinal puncture and ofttimes this comment is made: "We don't want the child to have a brain tap." In the past, under these circumstances, we were dependent upon the clinical course of the disease and, therefore, a small proportion of cases had undetermined diagnoses.

The sedimentation rate aided in ruling out uncomplicated virus diseases from those of bacterial origin and has been a constant comfort in the approach to the diagnosis where spinal punctures were refused. Recently Rosin[1] called attention to the marked variability in the sedimentation rate and white blood count in poliomyelitis.

Method of Determination. The Westergren method of sedimentation rates was used, the normals for this method being 0 to 15 mm. for males and 0 to 20 mm. for females in the 1st hour. Two determinations were done on each patient. 0.2 cc. of a 3.8% sodium citrate plus 1.8 cc. of blood were used. The first sedimentation rate was performed between the 2nd and 20th day from the onset of the illness, while the second was done from the 7th to the 30th day from the beginning of the disease. The average duration of time between the 2 determinations was 7.8 days.

Results of Sedimentation Rate Determinations. Among the first 100 cases we determined sedimentation rates on 76 as noted in Table 1. The rates in uncomplicated cases were practically all normal on entrance and also after the end of 1 week. Of the 5 bulbar types, including those *in extremis*, 3 had a normal rate. Of the 32 spinal types, only 5 presented a slight elevation of the rate, 1 of which had a slight elevation after the 1st week. In 14 of the 39 non-paralytic poliomyelitis cases there was an elevation of the rate on one or both examinations. It can readily be noted that there was no appreciable difference in the rates on the first or second examinations.

In this series of 76 cases, only 21 showed an increase in either or both determinations and 11 of these had elevations of from 1 to 4 mm.—a negligible increase. The remaining 10 cases had elevated rates from 5 to 25 mm. above the normal value, and 4 of these cases had concurrent disorders to account for the high elevation.

Case 1. A 56 year old female whose death occurred 24 hours after the second test was done. The second test showed an elevation of 7 mm. above the normal, and this could be explained by the fact that at autopsy pulmonary infarctions were found due to congestive heart failure.

CASE 2. A 5 year old girl. The first specimen was 24 mm. above the normal and the second 6 mm. Her spinal fluid showed 400 cells per c.mm., 81% of which were polymorphonuclear cells. In addition to poliomyelitis, a marked rhinopharyngitis was present.

CASE 3. A 12 year old boy; bulbar type. A marked cervical adenitis was noted, due to a superimposed bacterial infection. This accounted for the elevation of 15 mm. in the first specimen and 8 mm. in the second.

extreme value in aiding us in the differential diagnosis.

The following illustrated cases, referred to the Health Department, had fast sedimentation rates which indicated the need of further investigation for proper diagnosis.

CASE 5. A 19 year old boy who complained of headache, nausea, and pain in the neck for 2 days. Poliomyelitis was suspected but ruled out on the basis of a 48 mm.

TABLE 1.—SEDIMENTATION RATES IN 152 CASES

No. cases	Normal rate (both samples)	Elevated rate (both samples)	Elevated to normal rate	Normal to elevated rate
Bulbar—5	3 (60%)	2 (40%)	0 (0%)	0 (0%)
Paralytic—32	27 (84.3%)	2 (6.3%)	1 (3.1%)	2 (6.3%)
Non-paralytic—39	25 (64.1%)	6 (15.4%)	8 (20.5%)	0 (0%)
Total—76	55 (72.4%)	10 (13.1%)	9 (11.8%)	2 (2.6%)

TABLE 2.—AVERAGE RISE IN 21 CASES WITH INCREASED SEDIMENTATION RATE

Paralytic		Non-paralytic		Bulbar	
First	Second	First	Second	First	Second
1.6 mm.	6.0 mm.	8.7 mm.	1.0 mm.	11.5 mm.	4.5 mm.

CASE 4. A 5 year old girl; paralytic type. The first specimen had a normal rate, while the second had an elevation of 15 mm. However, the second sedimentation rate was done only 18 hours before she expired, so that the patient was, at that time, *in extremis* with pulmonary involvement.

Thus there were only 6 cases in the whole series in which an increased sedimentation rate could not be explained.

White Blood and Spinal Fluid Counts. The white blood counts of all cases varied between 3000 and 16,000. At no time was there a marked polymorphonuclear leukocytosis in the differential picture. The uniformity of the sedimentation rates was not influenced by the slight leukopenia nor the slight leukocytosis. Our records reveal variable spinal fluid cell counts of 18 to 650 white blood cells per c.mm. There was no appreciable relationship between the white blood count and the spinal fluid cell count.

Discussion. Although it is apparent that the sedimentation rate is not pathognomonic in the diagnosis of poliomyelitis, yet it is not erroneous to state that the sedimentation rate is quite constantly within normal range. It has proved of

sedimentation rate. The case was later diagnosed as a streptococcic infection of the mesopharynx.

CASE 6. A boy 7 years old who complained of pain in his right knee and calf muscles. His temperature varied from 99.6° to 101° F. A sedimentation rate of 45 mm. was an aid in excluding poliomyelitis. The case proved to be rheumatic fever.

CASE 7. A 2 year old boy who complained of pain in the left heel on pressure. Six weeks previously his foot had been struck. Subsequent to this he began to develop a limp, though there were no external signs of injury. He also complained of weakness in the right forearm. The sedimentation rate of 96 mm. excluded poliomyelitis from the diagnosis. Roentgen rays and further investigation revealed osteomyelitis of the left acetabulum.

Conclusion. 1. It is apparent from our experience that the uncomplicated disease poliomyelitis is represented by a fairly constant, normal sedimentation rate.

2. The sedimentation rate is an aid in the differential diagnosis of poliomyelitis from the bacterial diseases.

3. There is no correlation between the white blood count, spinal fluid cell count, and the sedimentation rate.

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THE EPIDEMIOLOGIC SIGNIFICANCE OF AMPLITUDES OF SEASONAL FLUCTUATION IN INFECTIOUS DISEASES

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Seasonal prevalence, one of the most constant characteristics of infectious diseases, has been generally attributed to the operation of some single factor—the favored one being seasonal variation in the mechanism by which the infectious agent is transmitted. But, so far, the exact reasons for the seasonal fluctuation observed in many diseases have not been clearly established.

In an earlier report in this Journal of seasonal variation in a number of infectious diseases,[2,6] certain differences in amplitudes of seasonal fluctuation were noted, which, in general, appeared to be characteristic of certain classes of disease.

"As judged from the magnitude of seasonal variations in infectious disease, in harborage of certain infectious agents and in physiologic functions, it is anticipated that the host-parasite interaction may be affected by season in two distinct ways. Seasonal changes in the host may have the simple effect of producing a seasonal variation in resistance to disease while not necessarily affecting the harborage or transmission of the infectious agent. On the other hand, both resistance to disease and resistance to infection (multiplication of the virus which in turn affects transmission) may be influenced by season. . . . Differences in the magnitude of seasonal variation in a number of infectious diseases affords some indication that the former may be a general rule in bacterial infection, and the latter in virus infections—a point, however, which will require further investigation."[2] The purpose of the present study is the further analysis of amplitudes of seasonal variation in a number of infectious diseases.

As has been discussed previously,[2] there is a wide divergence among the seasonal curves of the common upper respiratory diseases in the same geographic area with respect to time of peak incidence, with marked differences between northern and southern states. Because of this northern-southern variation, and because of certain exceptions in one or the other locality, data from 2 northern states, Massachusetts and Connecticut, as well as from 2 southern states, Alabama and Mississippi, have been considered in this study. The respective total populations of these combinations are roughly comparable.

The annual percentage distribution of cases by months of the epidemic years (the 12 month period beginning with the month of lowest incidence) for each of the common upper respiratory diseases was averaged over a period of 14 epidemic years covering the period 1925–1939.[6] By this method, years of high and low incidence are given equal weight in the final mean percentage distribution. Since a single year of very high incidence could alter the shape of the curve of seasonal distribution for an entire period,[1] curves of the seasonal distribution of cases in years of high, low, and intermediate incidence were compared. These comparisons indicated that the shape of the curves used in this study were not the reflection of excessively high or low years, but, in general, were characteristic of the various diseases throughout the period.

In order to facilitate comparison of amplitudes of seasonal variation alone, without regard to differences in the periods or phases in the seasonal curves of the different diseases, the mean annual percentage distribution curves all have been set forward or back the number of months required to make their periods and phases coincide.

in both the northern and southern states (Charts 1 and 2). Furthermore, as judged by the amplitude of seasonal variation, all upper respiratory diseases can be classified under 3 types of seasonal curves: 1 type of curve with low amplitude composed entirely of diseases of bacterial etiology; a 2nd of intermediate amplitude composed of 2 bacterial diseases and a single

TABLE 1.—DISEASES GROUPED ACCORDING TO AMPLITUDE OF SEASONAL VARIATION

	AMPLITUDE		
ETIOLOGY	LOW	INTERMEDIATE	HIGH
Upper Respiratory Bacterial	Meningitis, Mass.-Conn. (Aug.-July) Meningitis, Ala.-Miss. (July-June) Whooping Cough, Mass.-Conn. (June-May) Whooping Cough, Ala.-Miss. (Aug.-July) Diphtheria, Mass.-Conn. (May-April)	Diphtheria, Ala.-Miss. (March-Feb.) Scarlet Fever, Mass.-Conn. (June-May) Scarlet Fever, Ala.-Miss. (March-Feb.)	
Upper Respiratory Virus		Poliomyelitis, Ala.-Miss. (Dec.-Nov.)	Poliomyelitis, Mass.-Conn. (Jan.-Dec.) Mumps, Mass.-Conn. (July-June) Mumps, Ala.-Miss. (July-June) Measles, Mass.-Conn. (Aug.-July) Measles, Ala.-Miss. (Aug.-July) Chicken-pox, Mass.-Conn. (June-May) Chicken-pox, Ala.-Miss. (June-May) *
Intermediary Transmission Group	Typhoid Fever, Mass.-Conn. (Nov.-Oct.) Typhoid Fever, Ala.-Miss. (Nov.-Oct.) Typhus Fever, Reg. Area (Jan.-Dec.) Malaria, Reg. Area (Jan.-Dec.)		

* Smallpox in the U. S. Registration Area conforms with this group.

In Table 1, the diseases considered are listed according to amplitudes of seasonal fluctuation, low, intermediate or high, and the months of setback used to make their periods and phases coincide in the graphs to follow are indicated.

On the basis of differences in the amplitude of seasonal variation, upper respiratory diseases, with certain exceptions to be discussed later, can be separated into 2 groups, 1 of bacterial, the other of virus etiology. The exceptions, as noted in Table 1, were diphtheria and poliomyelitis in the southern states, and scarlet fever

virus disease (Chart 2); and a 3rd of high amplitude composed entirely of diseases of virus etiology. As can be seen in Charts 1 and 2, there is little difference in amplitude between curves for the respective diseases in northern and southern states, except diphtheria and poliomyelitis. Further selected comparisons indicated that the differences in amplitude between upper respiratory diseases of bacterial and virus etiology shown here were the same when data from the U. S. Registration Area[8] were used. Also, in Chart 2, the data on certain diseases of in-

termediatory transmission are treated in the same manner. The amplitude of the seasonal curves of this group of diseases is of the same order as that of the bacterial and virus upper respiratory diseases comprising the intermediate curve of the upper respiratory group.

In order to facilitate further analysis, the mean of each of the 4 groups of curves was determined. A comparison of the means of the bacterial and virus upper respiratory diseases (Chart 3) reveals the striking difference in amplitude, the ratio of low to high for the virus group (1:9.7) being more than 4 times that of the bacterial group (1:2). The rate of increase of the mean bacterial upper respiratory curve follows an arithmetic progression, suggesting simple numerical variation. The mean curve of the intermediary transmission group, as would be expected in phenomena conforming to the laws of mass action, exhibits a geometric increase. Similarly, the rate of increase of the mean virus upper respiratory curve also is more nearly geometric.

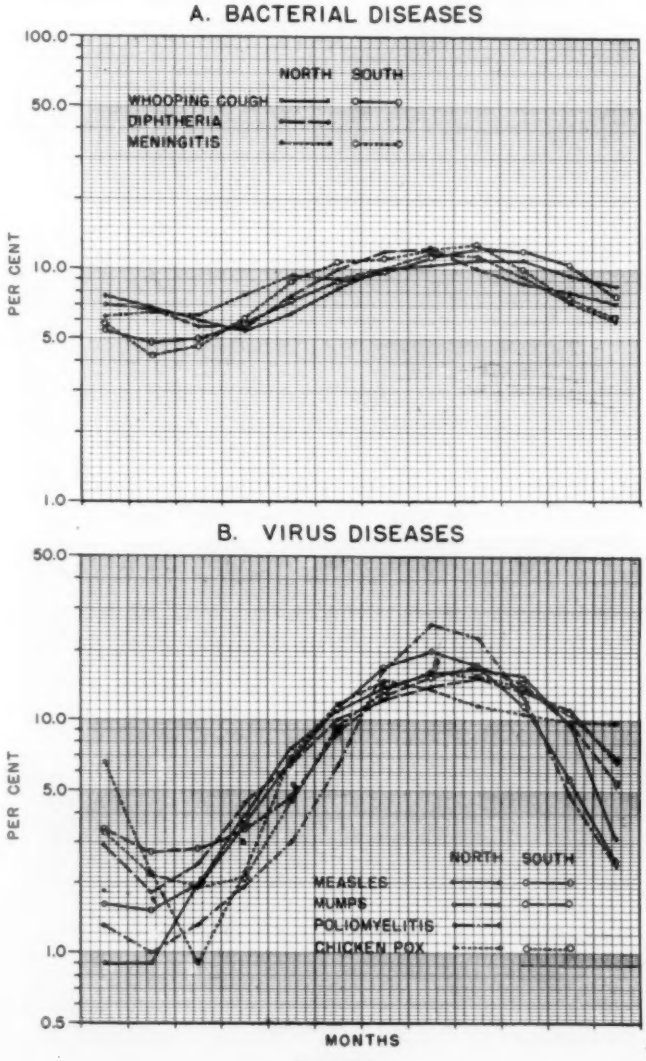

CHART 1

When the relative incidence of a disease, or a group of diseases, is plotted logarithmically against time the curve fits the equation:

$$\text{Log } D_1 = A + a \sin x$$

Then, if the relative incidence of a second disease or group of diseases with the same period and phase, but with a larger amplitude due to a simultaneous variation is plotted; the curve fits the equation:

$$\text{Log } D_2 = B + b \sin x$$

Then the receptivity function of the 2 curves is:

$$\frac{D_2}{D_1} = \frac{e^{(B + b \sin x)}}{e^{(A + a \sin x)}}$$

or,

$$\frac{D_2}{D_1} = e^{[(B - A) + (b - a) \sin x}$$

The logarithm of this function is the exponent of the Napierian base, which represents the difference of the 2 curves as plotted on

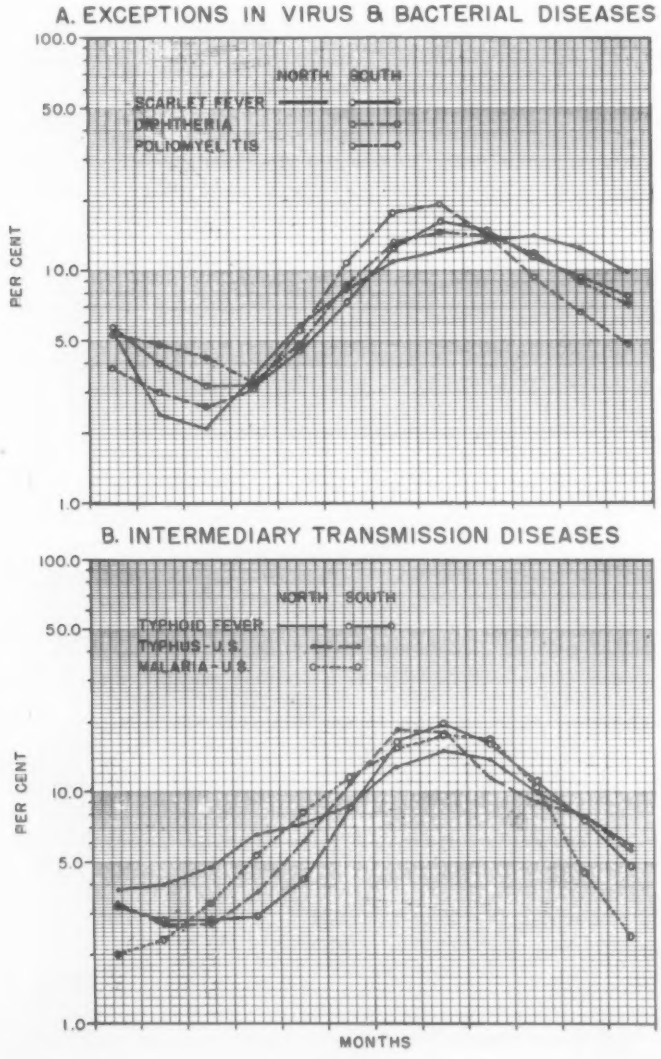

CHART 2

logarithmic paper. The amplitude of this difference can be determined by measuring the differences at the corresponding points on the 2 curves.

More simply, if the mean bacterial curve is subtracted logarithmically from the mean virus curve, the differences totalled and re-percented, the resulting curve represents the difference in amplitude between the mean bacterial and virus curves. The difference in amplitude between the mean bacterial and mean virus curves is almost identical with the mean curves for the intermediate group of upper respiratory diseases, and the group of diseases where transmission is intermediary as well (Chart 3). In other words, the amplitude of the mean virus curve is equal to the combined amplitudes of the bacterial upper respiratory and intermediary transmission groups of diseases.

The lack of knowledge as to the frequency and extent of virus harborage in most diseases of viral etiology precludes

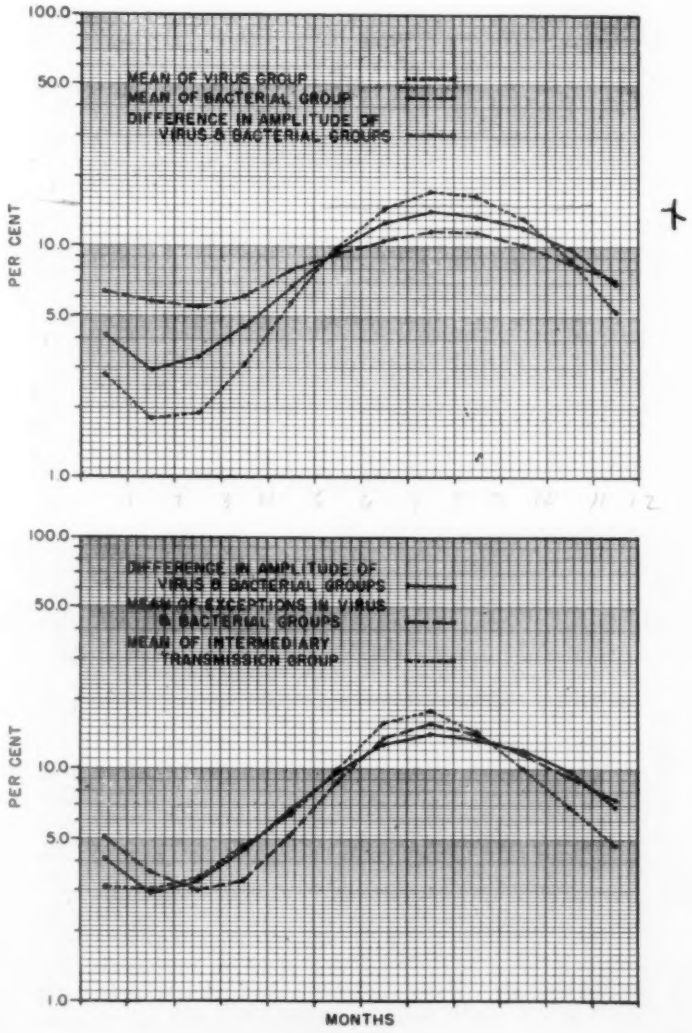

CHART 3

any discussion as to the stability of the dissemination rate of virus infection through healthy carriers, or perhaps more strictly in the case of virus infection, through subclinical infection.

However, data are available which indicate that the incidence of bacterial upper respiratory disease varies with season in spite of little or no seasonal fluctuation in the incidence of healthy carriage of the respective microörganisms. Meningococcus meningitis, for example, exhibits the amplitude of seasonal variation characteristic of the group of bacterial diseases in the face of no corresponding fluctuation in the meningococcus carrier rate. In other words, the attack rate in meningococcus carriers follows a seasonal variation of the same amplitude as that of the incidence of meningococcus meningitis, which is that of the bacterial upper respiratory diseases as a group[7] (Chart 4). It therefore appears that seasonal variation in meningitis may be determined by the

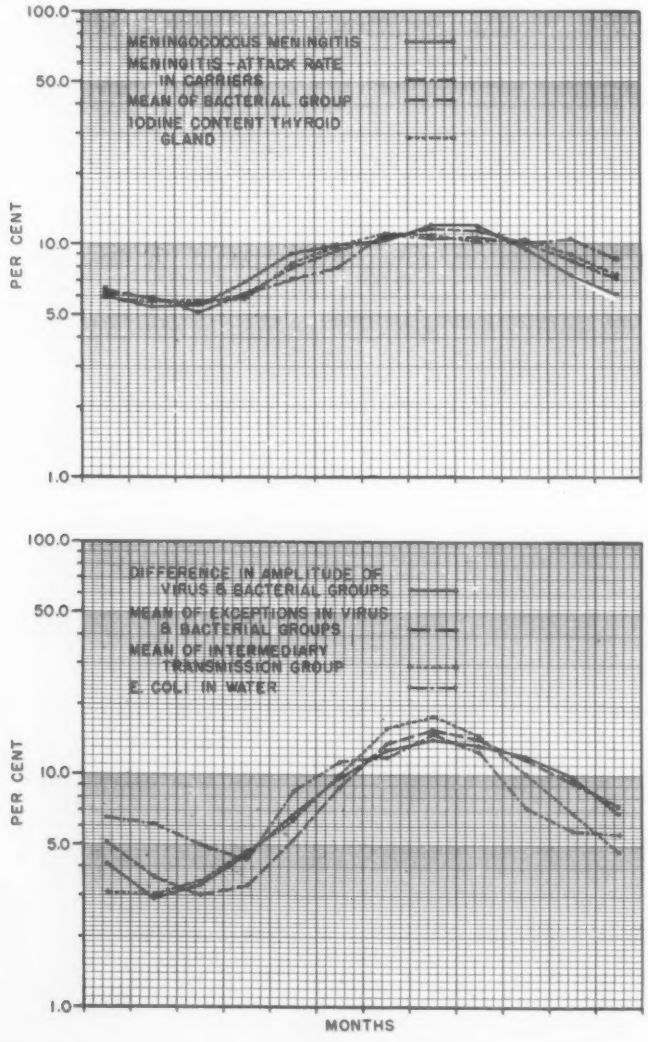

CHART 4

operation of the single factor of seasonal variation in susceptibility to the clinical disease.

In this connection it might be pointed out that the amplitude of a number of seasonal variations in physiologic processes is of the same order as that of seasonal variation in the bacterial group of infections. For comparison, the seasonal variation in the iodine content of the thyroid gland[4] is included in Chart 4.

In the intermediary transmission group of diseases (typhus and malaria, for example), on the other hand, seasonal variation is generally considered to be determined primarily by the bionomics of the vector rather than seasonal variations in the host. Typhoid fever is included in this group since its seasonal variation is generally considered to be the result of seasonal variations in opportunities for transmission. That this may be so is suggested, for example, by the seasonal variations of *E. coli* in water samples collected at various distances from the source of pollution in the Illinois River[5] (Chart 4).

The fact that diphtheria and poliomyelitis in warmer climates, and scarlet fever in both warm and cool climates have amplitudes of seasonal fluctuation of the same order as that of the intermediary group, in no sense infers intermediary transmission for these diseases. In the case of the diseases propagated by intermediary transmission, seasonal variation would appear to be due to fluctuation in the extra-human virus reservoir. A similar seasonal variation in a human virus reservoir would be expected to exhibit the same geometric amplitude of seasonal variation.

Since the amplitude of seasonal variation in the virus group of upper respiratory diseases is equal to the combined amplitudes of seasonal variation in the bacterial group (attributed to variation in susceptibility alone) and that of the intermediary transmission group (attributed to variation in virus reservoir), seasonal fluctuation in the virus upper respiratory group would appear to be the result of combined activity of the 2 factors—variation in susceptibility and variation in the human virus reservoir.

The explanation for the exceptions to the rule which applies in general in the amplitude of seasonal fluctuation in virus and bacterial diseases transmitted by direct contact is not clear. However, the diseases in which exceptions occur differ in certain respects from the groups to which they belong, and it is conjectured that the exceptions in amplitude of sea-

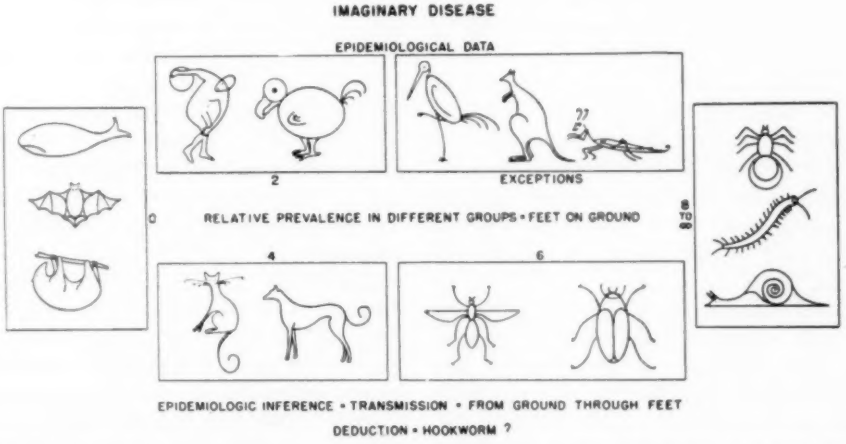

CHART 5—Illustrating the relative prevalence in an imaginary disease that occurs in 3 main groups in proportion to the number of legs of each individual of each group.

sonal fluctuation in them may in some way be accounted for by these differences.

In bacterial diseases where the rule is a seasonal fluctuation of low amplitude, it is inferred that a simple seasonal variation in susceptibility to frank disease upon infection is the explanation. In scarlet fever and diphtheria where the exceptions occur, toxin production is a part of the disease picture. The question is raised whether or not a seasonal variation in toxin production is involved. If such were the case, it would be expected that the amplitude of seasonal fluctuation would be the greater one determined by seasonal variation in the potential reservoir of infection, rather than the lesser one which can be best accounted for by seasonal variation in susceptibility to a "constant" reservoir of infection.

Of the group of virus diseases considered in this study, poliomyelitis is the only one in which there is a diminution in the frequency of frank disease in those exposed to the causative agent as warmer climates are approached (as is true of both diphtheria and scarlet fever). In cooler climates, there is a greater amplitude in seasonal variation in the host which, it is inferred, affects not only seasonal variation in susceptibility to frank disease, but also seasonal variation in the potential reservoir of infection (resulting from seasonal variation in multiplication of virus). The question is raised whether or not the exception to the general rule in virus diseases, in the case of poliomyelitis in warmer climates, may not be due in some way to the fact that poliomyelitis has the seemingly paradoxical characteristic of being a disease of the warmer seasons, but of cooler climates.

The amplitude of seasonal variation in scarlet fever, north and south, and of diphtheria and poliomyelitis, south, is equal to the seasonal fluctuation in the bacterial diseases as a group combined with a second amplitude of the same order. It seems, then, that the seasonal fluctuation of scarlet fever and diphtheria may be determined by variations of the same order in the virus reservoir and susceptibility. In the case of scarlet fever, this is substantiated in part by the observation that the Group A streptococcus carrier rate, unlike the meningococcus carrier rate, has a seasonal fluctuation of the same order of amplitude as that of the bacterial upper respiratory disease group,[3] and the now generally accepted fact that production of erythrogenic toxin by the streptococcus varies at different times in different places. It is perhaps more than coincidence that diphtheria, the other exception to the rule for the bacterial upper respiratory disease group, also is a disease in which the production of soluble toxin plays a rôle. It might be postulated that the difference in amplitude between northern and southern diphtheria and northern and southern poliomyelitis is the result of a more pronounced effect of seasonal change on the virus reservoir in cooler climates. This, together with the lesser range of fluctuation in physiologic function in warmer climates, might affect the differences between northern and southern amplitudes.

Summary. The amplitudes of seasonal fluctuation in a number of infectious diseases all fall into 1 of 3 types of curves. The first of these is a curve of low amplitude in which the progression is arithmetic in type. This suggests that in this group of diseases, amplitude of seasonal fluctuation is determined by some simple numerical variable. The close correspondence between this curve and those of a number of seasonal variations in physiologic functions, as well as the close correspondence with the curve representing seasonal variation in attack rate in carriers in meningitis, suggests that the amplitude of seasonal variation in upper respiratory contact bacterial infections may be determined in the main by seasonal variation in susceptibility to infection under a rate of exposure which does not necessarily follow a corresponding seasonal variation.

The second type of seasonal variation in which the progression is roughly geometri suggests the operation of a factor such as

seasonal variation in virus reservoir. This type of curve is seen in certain exceptions to the rule in upper respiratory bacterial and virus diseases, and is of the same order of amplitude as that exhibited by diseases transmitted through intermediary reservoirs, in some of which seasonal variation is believed to be determined in the main by variation in the virus reservoir.

The third type of seasonal curve is one of high amplitude and is equal to the combined amplitudes of the other 2 types of curves. This type of curve is characteristic of virus diseases transmitted directly from human to human, and the inference is made that the amplitude of seasonal fluctuation in these virus diseases is determined by a seasonal variation in susceptibility to infection, which accounts for the smaller part of the seasonal variation in disease (arithmetic) and combined with it seasonal variation of the same period and phase in multiplication of virus, which, in turn, affects transmission in geometric fashion. That susceptibility to infection and "susceptibility to harborage, multiplication and transmission" may be associated is manifest in the epidemiologic behavior of such virus diseases as measles and smallpox.

Perhaps the 3 amplitudes seen in different groups of diseases in exact multiples, and the idea that they are the result of a single influence (season) affecting simultaneously one, two or three factors involved, can be most simply illustrated by reversing the phenomenon and the line of reasoning to an epidemiologic chimera where the curves represent an imaginary "disease" occurring in 3 main groups of critters in proportion to the number of legs of the individuals in each group, and in certain exceptions according to the number of feet on the ground. The analogy with still other amplitudes can be extended on the one side to those that do not put their feet on the ground, and do not have the disease; and on the other side to those with many legs and much of the disease; all the way from the whale, with no feet and no disease at all, to the snail, all foot and all disease. (Chart 5.)

Conclusion. Three distinct patterns of amplitude of seasonal variation are found in a number of infectious diseases. In upper respiratory bacterial infections as a group, the amplitudes suggest the operation of a single arithmetic variable consistent with seasonal variation in susceptibility. In a second group, comprising diseases transmitted by intermediary means, the amplitudes are consistent with seasonal variation in the virus reservoir. In a third group, comprising upper respiratory virus infections, the amplitudes lead to the inference that both seasonal fluctuation in susceptibility in the human virus reservoir are determinants.

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PENICILLIN TREATMENT OF ACUTE SYPHILITIC NEPHROSIS AND IRITIS

REPORT OF A CASE*

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AMONG the visceral manifestations of early syphilis the acute nephrotic syndrome is well recognized.[1–3] Although the older methods of treatment usually produced satisfactory results when properly employed, no reports have appeared dealing with the effect of penicillin on this aspect of syphilitic infection. This brief paper reports an instance of secondary syphilis complicated by acute nephrosis and iritis in which penicillin was the sole antisyphilitic agent employed.

Case Report. A 29 year old Negress (J. H. H. 307289) was first seen in the Wilmer Eye Clinic on Nov. 15, 1943, because of dimness of vision due to an inflamed, painful right eye of 2 weeks' duration. Pupillary reactions were normal in both eyes and the media were clear. Uncorrected visual acuity was diminished on the right (20/40−1), 20/20 on the left. A diagnosis of conjunctivitis was made, irrigations were prescribed, and she was told to return in 3 days. She was seen again 1 week later in the clinic; in the interim it was found that her blood serologic test for syphilis was positive. Questioning revealed that a blood test done in March, 1942, had been negative for syphilis but that she had since been promiscuous in her relations. Four months before, a small pimple had appeared on her genitalia but this had spontaneously subsided in a few days. No skin rash, alopecia, adenopathy, or dysuria had been observed, but a severe sore throat, present 4 weeks previously, had responded to symptomatic treatment.

Examination disclosed that on the right side the eyelids were edematous; photophobia and lacrimation were extreme. Severe palpebral and bulbar conjunctival injection was seen and the deep scleral vessels were dilated. Although the cornea was described as clear by the eye consultant and no synechias were noted, the pupil was large and fixed to light (Fig. 1, *A*). An aqueous ray was present due to numerous circulating points in the anterior chamber (slit lamp examination). The left eye was normal in appearance and pupillary reactions were prompt. Uncorrected visual acuity was further diminished in the right eye (20/50 + 1) but still 20/20 on the left. The oropharyngeal mucous membrane was hyperemic but no mucous patches were seen. Submandibular adenopathy on the right and slight generalized lymph node enlargement were reported. There was a minimal degree of pitting pretibial edema bilaterally. Faint red, slightly pigmented macules were seen on both soles but no other cutaneous lesions characteristic of secondary syphilis were found. The neurologic examination was negative.

Laboratory studies disclosed anemia (13.3 gm. of hemoglobin per 100 cc. of blood) but an otherwise normal hemogram. Blood serologic tests for syphilis were positive, the Eagle flocculation titer being 32 units. Cerebrospinal fluid contained 40 leukocytes per c.mm. and 25 mg. of protein per 100 cc. of fluid. The Wassermann reaction was positive with as little as 0.6 cc. and the colloidal mastic curve was 4311000000. The specific gravity of a voided urine specimen was 1.018. Four-plus albumin was present but a qualitative copper-reduction test was negative. A few erythrocytes and 4 to 6 leukocytes per high power field were seen. On the basis of these findings the patient was admitted to the hospital for the experimental penicillin therapy of secondary syphilis complicated by acute diffuse iritis and the nephrotic syndrome.

The patient was in the hospital 4 days

* The work in this paper was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and The Johns Hopkins University.

before specific therapy was instituted; during this observation period the edema of the lower extremities completely subsided. She weighed 72.1 kg. (159 pounds) on admission to the ward. The blood pressure was 118 mm. of mercury systolic and 80 mm. of mercury diastolic. A culture of catheterized urine was sterile. A test of urea clearance done at this time was reported as 110% of normal standard and 97% of normal maximum clearance. Phenolsulfonphthalein excretion was good, 15% of the dye being recovered in 15 minutes and a total of 90% in 2 hours. Twenty-eight mg. of non-protein nitrogen and 242 of cholesterol were present per 100 cc. of blood. Blood chlorides, urea nitrogen, calcium and phosphorus levels were normal. Total serum protein was 6.88 gm. per 100 cc. of blood and the albumin-globulin ratio was 0.87 (Fig. 2). During her first 5 days in the hospital the daily excretion of albumin in the urine rose rapidly from 5 gm. (2.3 gm. per liter) on the day of admission to 20 gm. (7.4 gm. per liter of urine). Hyaline and granular casts were observed in small numbers during this pretreatment period but no erythrocytes were seen. The specific gravity of the urine was 1.025 on admission, a level not exceeded at any time.

Penicillin therapy was begun on the 5th hospital day (Nov. 29, 1943). Sodium penicillin, 10,000 Oxford units, in aqueous solution, were injected intramuscularly every 3 hours day and night for 60 doses, a total of 600,000 units in 7.5 days. This dosage schedule was selected on an entirely experimental basis. There was no Herxheimer reaction. After the 1st day of treatment the conjunctival injection was appreciably less and ocular pain had significantly decreased. By Dec. 2, lid edema had almost disappeared and blepharospasm had diminished (Fig. 1, *B*). Re-examination with the slit lamp 4 days later showed only a questionable aqueous ray but uncorrected visual acuity remained 20/50 in the right eye; haziness of vision was still a complaint. By Dec. 10, the right eye was said to be completely well; no ocular congestion or subjective symptoms remained.

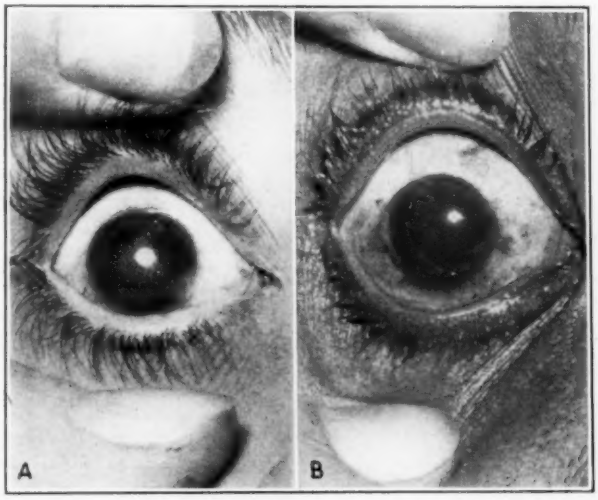

FIG. 1, *A*.—Right eye prior to treatment showing diffuse opacity within the anterior chamber. *B*, On the 4th day of penicillin therapy resolution of opacity is apparent. No residuals were found 708 days after the start of treatment.

These clinical findings paralleled in a remarkable manner the course of the syphilitic nephrosis, well illustrated by the diminution in the amount of albumin lost daily in the urine as shown in Figure 2. The total fluid and sodium chloride intake was not curtailed at any time. After the 2d day of penicillin treatment casts were not seen in any specimen of urine. On the 4th and 6th days of treatment counts of 2 and 4 erythrocytes per high power field were reported but hematuria was not subsequently noted. The specific gravity of daily urine specimens

varied from 1.019 on the day treatment was started to 1.009 with an average of 1.013. No significant diuresis occurred, the maximum daily urinary output (3725 cc.) being on the 11th day after the initiation of treatment; intake and output were comparable throughout. Body weight fell to 70.3 kg. (155 pounds) on the 2d day of therapy but at the time of discharge she weighed 73 kg. (161 pounds).

clearance was 95 and 86% of normal standard clearance (normal tests).

Spinal fluid taken at the end of the hospital stay contained only 4 leukocytes per cmm. of fluid and the protein content was unchanged. The Wassermann reaction was now negative in all dilutions, however, as was the colloidal mastic curve. The blood serologic titer underwent a series of interesting changes. The titer was 32 Eagle units

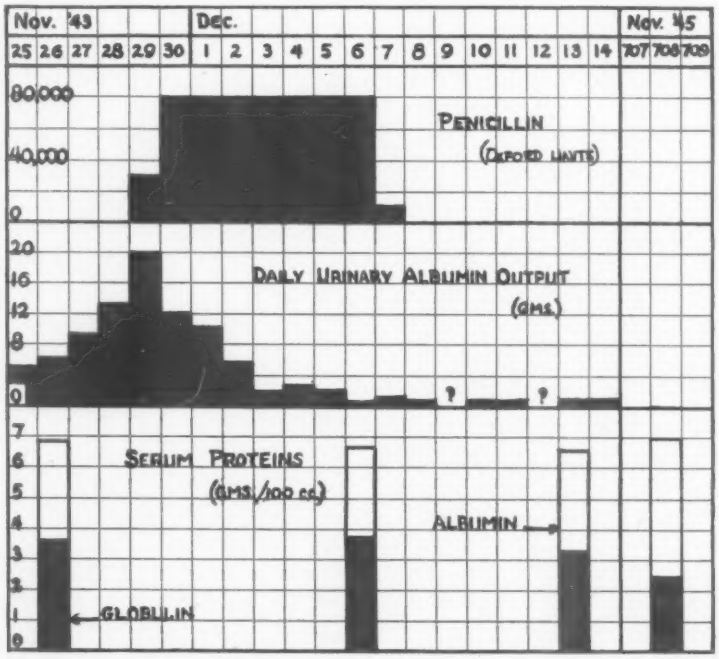

FIG. 2.—Effect of penicillin on blood and urine findings in acute syphilitic nephrosis.

Daily blood pressure determinations were, without exception, lower than the admission one; the average systolic pressure during her hospital stay was 102.3 mm. of mercury, whereas the mean diastolic pressure was 68.9 mm. of mercury. The hemoglobin content of the blood was essentially unchanged during her stay on the ward and non-protein nitrogen levels at no time exceeded 32 mg. per 100 cc. of blood. Prior to discharge the total serum proteins had fallen to 6.56 gm. per 100 cc. of blood, but the albumin-globulin ratio was greater than unity (1.06). Phenolsulfonphthalein excretion was reported as 40% in 15 minutes with a total of 80% of the dye being recovered in 2 hours; urea

prior to treatment; it rose to 128 units on the 6th and to 256 units on the 14th day after the start of therapy. The next examination, done 114 days after penicillin was begun, yielded an Eagle titer of 4 units; at 142 days a positive reaction was obtained with whole serum only (titer of 1). By 163 days the blood serologic test was negative and remained so in each of 8 subsequent tests performed at various intervals, the last one being on June 20, 1945, 570 days after the start of treatment.

On Nov. 5, 1945, 708 days after her first penicillin, this patient was readmitted to the ward for evaluation. She appeared to be in excellent general health and her bod

weight was 77 kg. (169.4 pounds). Blood pressure was 116 mm. of mercury systolic and 90 mm. diastolic. According to an eye consultant (Dr. Joseph S. Haas) the anterior chambers were of average depth and were optically inactive. The pupils were round, equal, and responded readily to light and accommodation. The iris stroma was similar in each eye. Uncorrected visual acuity was 20/20 bilaterally. The final impression was "complete healing of right iritis with no residuals."

From the laboratory standpoint the improvement had been equally well sustained. Two blood serologic tests for syphilis were negative. The spinal fluid contained 2 leukocytes per cmm. and 17 mg. of protein per 100 cc. of fluid. The Wassermann reaction was negative in all dilutions as was the colloidal mastic test. Microscopic examination of the blood disclosed a normal hemogram except for hypochromic anemia: 4,830,000 erythrocytes per cmm. of blood but only 11.8 gm. of hemoglobin per 100 cc. The serum proteins totalled 7 gm. per 100 cc. of blood and the albumin-globulin ratio was 1.60 (see Fig. 2). Determinations of nonprotein nitrogen, total cholesterol, and blood urea nitrogen were normal.

An urinalysis on the day of admission to the ward contained a faint trace of albumin but was otherwise normal; three subsequent analyses were entirely negative. A culture of urine was reported as containing *Microærophilus alpha streptococcus* which was regarded as a contaminant. Tests of kidney function were entirely satisfactory. Ability to dilute and concentrate urine was demonstrated by samples with specific gravities of 1.002 and 1.023 respectively. Urea clearance was 130% of normal standard clearance. Results of the phenolsulfonphthalein test were excellent; 40% of the dye was excreted in 15 minutes, a total of 95% in 2 hours.

Discussion. The diagnosis of nephrosis depends clinically on the presence of albuminuria, transient edema, changes in the serum proteins, especially the albumin fraction, and either absent or non-persistent hypertension or nitrogen retention. Casts in the urinary sediment are seldom numerous and erythrocytes are rare. Such tests of kidney function as urea clearance and phenolsulfonphthalein excretion are characteristically normal.[5] The most common occurrence suggestive of renal damage in syphilitic patients is a simple, slight albuminuria unaccompanied by other evidences of nephropathy. Some degree of albuminuria was found, for example, in 7.1% of 1040 patients with syphilis studied with regard to kidney involvement. No patients with primary lesions but 5 of 61 (8.2%) with secondary manifestations had albumin in the urine.[2] A small percentage of these progresses to the clinical picture previously described, indistinguishable from idiopathic nephrosis except that appropriate antisyphilitic treatment causes a diminution or disappearance of the albuminuria.[1]

Prior to the advent of penicillin each of the accepted antisyphilitic drugs had been used singly and in various combinations with success. Herrmann and Marr[2] remark, however, that "each drug has been noted in some case or another to have increased the albuminuria or other signs of renal involvement, and especially has this been so when the drug was administered in its usual doses. It must be remembered that in all antisyphilitic therapy the damaged renal tissue of syphilitic nephropathies is more vulnerable than normal kidney parenchyma." This has been further emphasized by Moore[4] who points out that large initial doses of the older drugs were known to provoke severe Herxheimer reactions which "may result with anuria, increasing edema and nitrogen retention, and even uremia." For these reasons, as in other types of visceral syphilitic disease,[6] the essentially nontoxic properties of penicillin recommend it highly. Although Herxheimer reactions are frequent in patients with early syphilis treated with this antibiotic substance, they are characteristically mild and it is felt that they may be safely disregarded because no additional chemical insult is imposed upon the injured kidney parenchyma.

The eye lesion in this patient is also of considerable interest for two reasons. Iritis has been the most important of the

ocular complications of early acquired syphilis, occurring in about 4% of all cases of secondary syphilis.[7] In this patient, the response to penicillin therapy was dramatic, the involved eye being objectively and subjectively well within 11 days after the start of treatment. Woods[7] has emphasized the tendency to ocular relapse in these patients following inadequate therapy by the older methods. Fortunately, with this antibiotic agent the entire treatment may be given during a short period of hospitalization; even irresponsible patients have a minimal opportunity to lapse. Although no evidence of ocular relapse was present in the patient here reported after a follow-up period of 708 days, the problem of the frequency of such occurrences in patients with penicillin-treated syphilitic iritis is one requiring statistical attack.

The efficacy of penicillin in acute syphilitic nephrosis and iritis is well illustrated in the case presented here. In the light of subsequent experience the experimental total dosage originally chosen of only 600,000 Oxford units would be considered inadvisable; several times that amount would now be employed. It is significant, however, that not only did that relatively small dosage produce rapid and sustained improvement in the complications but it apparently cured the underlying syphilitic infection itself, as evidenced by clinical and serologic negativity almost 2 years after therapy.

Summary. A patient with secondary syphilis complicated by acute nephrosis and iritis is reported. Treatment was experimental and consisted of the intramuscular administration of 600,000 Oxford units of sodium penicillin in 7.5 days. Dramatic immediate and sustained improvement of both complications ensued. The underlying syphilitic infection itself was apparently cured, as judged by clinical and serologic negativity 708 days after the initiation of treatment. The advantages of penicillin over the older methods of therapy are discussed.

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SALMONELLA SUIPESTIFER INFECTION IN CHILDREN

A Report of Eighteen Cases

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Quite a number of isolated cases of *Salmonella suipestifer* infection among infants and children have been reported,[8,11,14,15,16,19,24,26,28,31] as well as outbreaks of food poisoning due to the Salmonella group, but relatively few articles have dealt with any appreciable number of cases.

In Harvey's[17] series of 21 cases there were 14 children, while Goulder *et al.*[14] reported 6 cases in children. Gajzago and Gottché's[12] report included 6 cases of this type of infections (with osteomyelitis in all 6), while Kuttner and Zepp[24] reported 7 such cases. During the past 8 years, 18 cases of *S. suipestifer* infections were admitted to this hospital. The average annual admission rate during this period was 2084 cases. It appears thus, that this disease is relatively rare in the Philadelphia area. The purpose of this paper is to report these 18 patients in some detail. Table 1 lists the important features of these cases.

History of the Illness. On the basis of the information obtained from the case histories, all of the cases seemed to be sporadic infections. None were of the so-called "food poisoning" type (more correctly termed Salmonella infections), where a common source of infection like contaminated food, could be found.[18,32,34] No other cases occurred in the same households as far as could be determined, nor were similar infections subsequent to the patient's return home from the hospital later reported in possible contacts.

Age. The range of age was between 4 months and 10 years. Only 2 of the children were over 2 years of age, while 1 child was 2 years old, and the remainder were under 2 years of age.

Signs and Symptoms. Gastro-intestinal symptoms: only 4 of the patients gave a history of vomiting, or vomited while ill in the hospital. There were only 9 patients who had diarrhea, 6 of a mild character, while 1 had diarrhea for 25 days. One had gross blood in the stools.

Fever. The average number of days of fever, with the exception of the patient who died, was 3½ days. One patient had fever for 24 days, but was not very ill.

Infection of the Respiratory Tract. There were 12 patients who had a nasopharyngitis on admission. Nine of the 18 cases had either unilateral or bilateral otitis media (suppurative) on admission, or before they recovered. Five cases showed pulmonary signs by physical examination, and 2 of these had bronchopneumonia as shown by Roentgen ray examination.

Course. There were 2 deaths among the group. One of these was found at postmortem examination to have bilateral polycystic kidneys. The other patient who died was a premature infant who had diarrhea 1 week prior to admission. The patient with petechiæ was acutely ill, while those patients with otitis media and infection of the respiratory tract were moderately sick. However, most of the patients were not very ill, and the disease in these ran a short, benign course. Of the 14 patients with positive blood cultures only 7 had diarrhea. Enlargement of the spleen was noted in only 3 patients, and none of the patients developed "rose spots."

Treatment. The therapeutic aspects of suipestifer infection, in common with those of most other infections produced by gram-negative bacilli, leave a great deal to be desired. Concerning the Salmonella organism there are available certain laboratory studies which would seem to point the way to the proper clinical approach. However, the limited number of clinical reports dealing with specific therapy do not permit a hopeful outlook concerning correlation between the results obtained in the test tube and in the patient.

Interesting studies, very largely of a laboratory nature, have been made relative to serums, vaccines, and bacteriophage in a variety of Salmonella infections.[2,23] Specific antisera against certain Salmonella organisms have been produced which will protect animals against infection or will prevent death in animals after the administration of otherwise lethal doses of organisms. Specific antisera are not generally available for use against suipestifer infection in the human. Vaccines in some instances yield high antibody titers and good evidence of protection, but because of the low incidence of the disease they find little application in clinical practice where treatment and not immunization is the usual problem. Mice can be protected against many types of Salmonella organisms by the use of specific bacteriophage, but results in humans are inconclusive and time is always required for the preparation of a specific phage.

Whenever suipestifer infection localizes, with abscess production, surgical drainage is indicated and is usually followed by satisfactory results.[8,33,37]

In vitro experiments indicate that both sulfadiazine and sulfathiazole are effective inhibitors of suipestifer, and that they are even bactericidal under certain specific conditions.[27,35] *In vitro*, suipestifer is the most susceptible of all the common Salmonella organisms.[27,35] In certain synthetic media either sulfathiazole or sulfadiazine in a concentration of 1 mg. per 100 cc. of media is lethal for suipestifer in 24 hours. However, in broth culture, to produce the same lethal effect, 10 to 50 times as much was required depending upon the broth used. This is but another example of the influence of substrate on chemotherapeutic effectiveness.[35]

If sulfathiazole or sulfadiazine is to be used in human suipestifer infections it would seem rational to utilize a drug capable of giving adequate blood levels and at the same time capable of maintaining a high concentration in the lumen of the bowel. This is based upon the fact that most cases are both septicemic and at the same or at some other time, enteric. Until recently it was believed that the combination of sulfathiazole and succinyl-sulfathiazole would most satisfactorily meet the above requirements. It is possible, however, that sulfathiazole alone is as effective as the combination.

In the present series of 18 cases, 12 received sulfonamide therapy and 6 had none. Of the 12 treated with sulfonamides, 8 received sulfathiazole only, 1 received succinyl-sulfathiazole only, and 1 received sulfadiazine, sulfathiazole, and succinyl-sulfathiazole. In addition, 1 patient received sulfathiazole and sulfaguanidine and 1 other received sulfathiazole and sulfapyridine. In comparing these 2 very small groups of patients no clinical effect upon the infection could be ascribed directly to the compound used. In terms of fever, symptoms, and cultures of the blood and stools, there was no significant difference between those treated and those not treated with sulfonamides. All cases received such supportive therapy of a non-specific nature as was required. The restoration and maintenance of electrolyte and fluid balance plus blood transfusion when it seemed indicated, were the basis for this supportive treatment. The group is obviously too small to permit judgment concerning the value of sulfonamide therapy. It is felt however that the use of sulfathiazole or sulfadiazine represents a rational chemotherapeutic approach to the treatment of suipestifer infection.

It is hardly possible to conclude any consideration of therapy of a bacterial disease without mentioning the effect of antibiotic substances. In general the available antibiotic substances are not effective against Salmonella organisms. The reasons for this lack of effectiveness are now rather well understood.[9,10,13,35] Penicillin is not effective against suipestifer not, indeed, against most pathogenic gram-negative species. Streptomycin has been shown to be effective in protecting mice against *Salmonella schottmülleri*.[22] Within proper dose ranges this protection is complete against otherwise uniformly lethal doses of the organism. The value of streptomycin in suipestifer infections remains to be determined.

Comment. The mildness and relative infrequency of gastro-intestinal symptoms is worthy of note. Only 9 patients had diarrhea, and this was of a mild character, except in the premature infant who died. The latter patient was the only one who had gross blood in the stools. In a report of 7 cases by Kuttner and Zepp,[25] 1 had a a nasopharyngitis, 1 had otitis media, 1 had acute tonsillitis and bronchopneumonia. None had diarrhea. In another report by Kuttner and Zepp[24] of 4 cases of *S. suipestifer*, 1 was admitted to the hospital with bronchopneumonia, and another had a nasopharyngitis; while the other 2 had pyarthrosis, but none of the cases had diarrhea.

Invasion of the ears and respiratory tract in *S. suipestifer* infections has been noted with varying frequency by various authors. Hormaeche *et al.*,[20] who made a comprehensive study of diarrhea due to the Salmonella group of organisms among infants and children, obtained 10.1% positive pharyngeal cultures in 152 cases. Included in these cases were 67 children with draining ears, and of these, there were 20.89% who had positive cultures from the aural discharge. These factors could be important as regards the spread of Salmonella infections in a hospital ward. Gouley and Israel[15] cited the literature on 14 sporadic cases. Of these there were 7 cases who had pneumonia. Bullowa[7] was able to isolate the causative organism from the sputum of a case of pneumonia due to *S. suipestifer*. Bosch[6] has stressed the increased incidence of *S. suipestifer* infections in the presence of pneumonia and malaria.

In spite of the high incidence of bacteremia among our patients (Table 1), no case developed evidence of localization of the infection such as osteomyelitis or arthritis. This was surprising in view of the many types of complications in *S. suipestifer* infections that have been reported.[8,11,12,14,15,16,19,21,24,26,28,29,30,31] In the other reports, bone and joint involvement seemed to be frequent. Harvey[17] stated that from his study of reported cases of *S. suipestifer* infections, bone and joint involvement occurred in about 20% of the total. All 6 of the cases reported by Gajzago and Gottché[12] had osteomyelitis. These authors collected the data from 34 cases of *S. suipestifer* in children that had been reported from various countries since 1920, and found that 12 of the 34 had osteomyelitis. The number of cases in these reports showing positive blood cultures seems fairly high, in light of the mildness of the clinical picture in most of the patients. Of the 71 cases collected by Harvey,[17] 44% had positive blood cultures, and 5 of the 6 children in Goulder's[14] series were positive. Bacteremia was present in only 10.34% of Hormaeche's[20] cases.

The bacteria are not difficult to grow from cases of bacteremia, but proper identification of the specific organism in Salmonella infections may, at times, be a difficult procedure. This is largely due to the presence of separate antigens in the body, in contrast to the flagella of the organism, and because the agglutination behavior for the 2 antigens is entirely different. Also, many of the organisms may exist in 2 phases, a specific phase, with flagellar antigens peculiar to itself, and a group phase, in which the flagellar antigens are common to many members of the Salmonella group of bacteria. *S.*

TABLE 1.—EIGHTEEN CASES OF SALMONELLA SUIPESTIFER INFECTION (SALMONELLA CHOLERÆSUIS) (HOG CHOLERA)

Case No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Age Y: Years	9	1	2	10	10	18	5	1	1½	4	1½	1	1½	17	10	9	6	1
M: Months	M	Y	Y	M	Y	M	Y	Y	Y	M	Y	Y	Y	M	Y	M	M	M
Sex	M	M	F	M	M	F	M	M	F*	F	F	F	F	F	M	F	M	F
Duration of fever (total)	6	11	5	24	3	7	3	18	15	8	4	15	4	–	2	1	2	16
Upper respiratory infection	+	+	+	+	–	+	+	+	+	+	+	+	+	–	–	+	–	–
Otitis media	+	–	+	+	–	+	–	+	+	+	–	+	–	+	–	–	–	–
P.E. lungs	R	R	R	Pn	–	–	–	–	Pn	R	R	–	–	–	–	–	–	–
Splenomegaly	+	–	–	–	–	–	–	–	+	–	–	+	+	–	–	–	–	–
Vomiting	+	+	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Diarrhea	+	–	–	+	+	–	–	+	–	+	+	–	+	–	–	–	+	+
Blood in stool	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+
Blood culture	+	+	+	+	–	+	+	+	+	+	+	+	+	ND	–	+	–	+
Stool culture	–	+	–	–	+	–	–	–	–	+	+	–	–	+	+	ND	+	–
Blood agglutination	ND	ND	+	+	ND	+	–	–	+	–	+	ND	+	ND	ND	–	+	ND
Recovered or died	Rec.	Rec.	D	Rec.	Rec.	Rec.	Rec.	Rec.	Rec.	Rec.	Rec.	Rec.	Rec.	Rec.	Rec.	Rec.	Rec.	D

R, râles; Pn, pneumonia (by Roentgen ray); ND, not done; Rec., recovered; D, died (bilateral polycystic kidneys at autopsy).

suipestifer, American type, can exist in both the group and specific phase, while *S. suipestifer*, European type, can exist in the group phase.

Goulder *et al.*[14] performed agglutination tests on the sera of normal individuals to determine if they had agglutinins for *S. suipestifer* and obtained negative results. However, high agglutination titers were found in most of the *S. suipestifer* cases, and this titer persisted for a period of time ranging from a few months to 6 years after the infection. Harvey[17] was able to find reported titers as high as 1 to 12,800, and in his series 88% of the patients had a titer higher than 1 to 320 by the 4th week. In 1 of these, a titer of 1 to 250 was still present 2 years after the illness.

Some of the fermentation characteristics of *S. suipestifer* and *B. paratyphosus* are shown in Table 2.

TABLE 2.—FERMENTATION REACTION OF BACTERIUM PARATYPHOSUS B AND SALMONELLA SUIPESTIFER

	B. paratyphosus B	*S. suipestifer*	
		American	European
Production of gas	+	+	+
Mannitol	+	+	+
Dulcitol	++++	++++	++++
Sorbitol	+	+	+
Inositol	++++	0	0
Maltose	+	+	+
Arabinose	+	0	0
Rhamnose	+	+	+
Xylose	++++	+	+
Trehalose	+	0	0
Dextrin	+	+	+
Litmus milk	Alk	Alk	Alk
Production of H.S.	+	0	−
Bitter rhamnose	++++	0	0
Stern glyceral	++++	0	0
d-tartrate	++++	+	+
Utilize citrate agar	+	0	0
Utilize tartrate agar	0	+	+

+, positive; 0, negative; ++++, variable or delayed fermentation.

* Bornstein, S.: The State of the Salmonella Problem, J. Immunol., **46**, 439, 1943.

Summary. Clinical and bacteriologic data on 18 sporadic cases of *S. suipestifer* infection are presented.

Vomiting occurred in only 4 patients, while there were 9 who had diarrhea. One of the patients had gross blood in the stools.

There were 12 patients who had an infection in the respiratory tract. Of these, there were 9 with otitis media, 2 with bronchopneumonia by Roentgen ray examination, and 3 others with pulmonary signs by physical examination.

None of the patients developed an infection in bones or joints. Of blood cultures, taken on all but 1 patient, 14 were positive in 17 cases. Stool cultures were done on all but 1 patient and 7 were reported as positive. Blood agglutination studies were made too infrequently to be of value.

There were only 2 deaths in the group. One of these had bilateral polycystic kidneys, while the other was a premature infant who had diarrhea at home for 1 week before admission.

Treatment of suipestifer infections include proper parenteral administration of necessary fluids and electrolytes in the more severe cases accompanied by diarrhea. The administration of sulfathiazole or sulfadiazine is indicated on the basis of experimental laboratory data, but in the series of cases here presented, it was not possible to demonstrate any well-defined effects which could be directly ascribed to the administration of sulfonamides. In general, the available antibiotic substances are not effective against Salmonella organisms. The effectiveness of streptomycin is currently under investigation in Salmonella infections. This substance seems more promising than compounds previously tested.

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THE INCIDENCE OF PALPABLE PULSATIONS IN CONVALESCENT TRENCH FOOT

AN ANALYSIS OF 500 PATIENTS AT AN ARMY GENERAL HOSPITAL

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THE criteria for a diagnosis of trench foot after the acute symptoms have subsided are not clearly defined. The diagnosis often depends solely on a reliable history. In the diagnosis of peripheral vascular diseases in general, palpation for pulsations of the peripheral arteries is an important clinical procedure and may give a great deal of information. An absent pulsation may be seen in spasm or as a result of organic changes in the palpated vessel. It may also indicate a normal anatomic deviation. In the course of studying some of the diagnostic criteria of convalescent trench foot we have been struck by the high incidence of good peripheral pulsations, often in the face of extensive damage and gangrene of the foot.

To investigate this clinical impression, the dorsalis pedis and posterior tibial pulsations of 500 soldiers hospitalized for trench foot at an Army General Hospital were studied. Each soldier was convalescing from either a moderate or an advanced degree of trench foot.* A moderate type was characterized by a typical history of exposure with skin and soft tissue changes but without evidence of gross gangrene. An advanced type was characterized by gangrene with subsequent loss of foot substance. There was an average interval of 6 months from the time of onset of the disease to the date of this study. The study was limited to white soldiers, and the average age was 25. The majority of the patients were from infantry units and prior to the time of hospitalization no soldier had complained of any significant circulatory disturbance of the lower extremities. The pulsations were graded as "palpable" or "not palpable." Where a pulsation was weak, faint, or a slight distance from the usual location it was considered palpable.

The findings are shown in Table 1. Of the 500 patients examined, 442 (88.4%) had a palpable right dorsalis pedis pulse and 58 (12.6%) an absence of this pulse. The right posterior tibial pulse was palpable in 486 (97.2%) and absent in 14 (2.8%). On the left side similar figures were obtained. The left dorsalis pedis pulse was absent in 72 (14.4%) and the left posterior tibial pulse was absent in 9 (1.8%). There was an absence of both dorsalis pedis pulses in 29 (5.8%) patients and an absence of both posterior tibial pulses in 4 (0.8%). An absence of both posterior tibial and dorsalis pedis pulses on the same side was found in only 3 patients. No patient of this series demonstrated absence of pulsations of both the dorsalis pedis and posterior tibial arteries of both feet.

A clinical study dealing with the presence of pulsations is not without error and is subject to certain criticism. In the first place, the detection of a pulsation depends to a large extent on the efficiency and experience of the examiner. Moreover, the environment in which the examination is performed can influence the results. A cold room, for example, can cause constriction of an artery rendering it barely palpable or impalpable. Age, sex and race are further variables. Emo-

* No attempt was made to differentiate between trench foot and frost-bite. It is generally agreed these 2 conditions are related and a similar mechanism operates in each.[5]

tional influences, such as seen in anxiety states, are important and may influence the caliber of a peripheral vessel. The physical condition of the patient at the time of the examination must also be considered. Such conditions as local deformities, varicosities, edema, and obesity may make it difficult to palpate a normally located vessel. Finally, the arterial supply of the human foot is normally subject to wide anatomic variations.[6,7]

With these limitations in mind, an attempt was made to correlate the incidence of dorsalis pedis and posterior tibial pulsations in the trench foot patients with a similar group of healthy soldiers. The same medical officer (J. J. S.) examined both groups and the same criteria for the presence or absence of a pulse were used. The control group was made up of 908 white soldiers picked for the infantry. The average age was 20. The examination was part of the processing for overseas assignment, and as far as could be ascertained, no soldier in this group had circulatory complaints affecting the lower extremities.

The absence of pulsations in the group of controls is comparatively shown with the trench foot patients (Table 2). The similarity of results is striking. No significant difference in the incidence of absent pulsations of the foot in the 2 groups was found.

Comment. Trench foot achieves special prominence in time of war. The clinical observation of extensive tissue damage in soldiers suffering from trench foot in the presence of good pulsations has long been known. Larrey, Napoleon's Surgeon General, in 1812,[3] noted that trench foot is not to be confused with ordinary gangrene. To quote: "I have seen examples where a greater or less part of the skin of the foot has been mortified without the vessels having lost their vitality." More recently, Lesser,[4] in a study of the casualties of the Attu campaign, reported: "In all cases the peripheral arterial pulses were of excellent quality." In Lesser's series there were 25 patients with extensive sepsis and gangrene.

Without going into the details of the pathogenesis of this condition, it is generally agreed that, initially at least, there are profound changes in the peripheral blood-vessels. Cold is a powerful vasoconstrictor both locally and reflexly.[5] During mild exposure to cold the chilled tissues require little oxygen and no damage is sustained on recovery. On prolonged exposure, however, there is anoxia and injury to the capillary walls resulting in increased permeability, exudation and

TABLE 1.—INCIDENCE AND ABSENCE OF PULSATIONS IN 500 PATIENTS WITH CONVALESCENT TRENCH FOOT

	Palpable		Not palpable	
	No.	%	No.	%
Dorsalis pedis (right)	442	88.4	58	11.6
Dorsalis pedis (left)	428	85.6	72	14.4
Posterior tibial (right)	486	97.2	14	2.8
Posterior tibial (left)	491	98.2	9	1.8
Dorsalis pedis (bilateral)	471	94.2	29	5.8
Posterior tibial (bilateral)	496	99.2	4	0.8
Dorsalis pedis and posterior tibial (same side)	497	99.4	3	0.6

TABLE 2.—TABULATION SHOWING ABSENT PULSATIONS OF THE FOOT IN 908 NORMAL CONTROLS AS COMPARED WITH 500 TRENCH FOOT PATIENTS

	Control		Trench foot	
	No.	%	No.	%
Dorsalis pedis (right)	114	12.6	58	11.6
Dorsalis pedis (left)	132	14.5	72	14.4
Posterior tibial (right)	20	2.2	14	2.8
Posterior tibial (left)	18	2.0	9	1.8
Dorsalis pedis (bilateral)	25	8.3	29	5.8
Posterior tibial (bilateral)	9	1.0	4	0.8
Dorsalis pedis and posterior tibial (same side)	5	0.5	3	0.6

edema. With restoration of temperature the arterioles relax and with the increased blood flow there is transudation of plasma and even of blood through the damaged capillaries. It is in this period of circulatory restoration that occlusion of the smaller vessels occurs with formation of red blood cell clots.[2] The smaller arterioles and veins may demonstrate, on pathologic examination, almost complete obliteration of their lumen. The larger arteries are rarely involved.[1]

instituted and he was eventually transferred to the United States. When seen at this General Hospital the first and second toes of the left foot presented a black gangrenous appearance. The right foot was essentially negative to examination. On March 20, under spinal anesthesia, the first and second distal phalanx of the left foot were amputated. Figure 1 demonstrates an occlusion of one of the smaller arterioles seen on microscopic section* of one of the amputated toes. It should be mentioned that in spite of the gangrenous changes the palpable

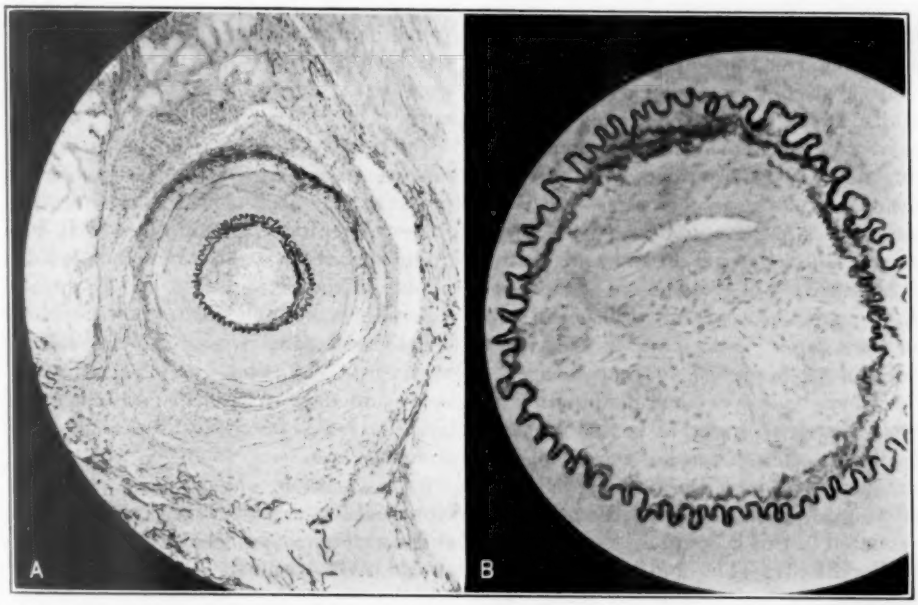

FIG. 1.—*A*, Photomicrograph of an occluded arteriole showing recanalization. Section taken from an amputated toe of a soldier suffering from severe trench foot. Orcein stain. (× 100.) *B*, Photomicrograph of same arteriole under higher magnification. (× 440.)

The following case history is illustrative:

Case Report. A 23 year old white Pfc. was admitted to the U. S. A. General Hospital, Camp Butner, N. C., on Mar. 1, 1945, with a diagnosis of trench foot severe, bilateral. Between Jan. 1 and Jan. 4, 1945, he was immobilized in a foxhole while taking part in combat near Bastogne, Belgium. During this period the soldier had no opportunity to change his socks or shoes. On arrival at an Evacuation Hospital both feet were swollen, discolored and lifeless. The standard treatment for trench foot was

pulsations of the foot of this patient were excellent. The dorsalis pedis and posterior tibial arteries were both full and bounding.

The effect of cold was experimentally studied by Talbott[9] in therapeutic hypothermia. Following exposure to this artificial type of cold one of the first effects observed was an obliteration of the peripheral venous channels so that it eventually became impossible to withdraw venous blood. As the hypothermia was continued constriction of the larger arteries occurred

* Lt. Matthew Block, M.C., A.U.S., performed the microscopic studies.

so that it was difficult to obtain a blood pressure reading. The blood pressure and pulse were unobtainable for several hours, yet there never was any evidence of a thrombus developing in the lumen of the artery as a complication.

Oscillometric studies in this condition reveal no abnormalities, since the oscillometer reflects the pulsation of the larger arteries. Trench foot is essentially a disease of the smaller arterioles and capillaries; and only in extreme cases are the larger arteries involved to the point of occlusion. An occlusion, therefore, of the dorsalis pedis or posterior tibial arteries in a patient who previously demonstrated good pulsations in these arteries would tend to speak against the diagnosis of the usual type of trench foot. It should be remembered that normally the arterial circulation of the foot is subject to wide variations. In a group of healthy soldiers recently studied,[7] over 13% demonstrated an absence of 1 or more pulses of the foot. However, it was extremely unusual to find an absence of both dorsalis pedis and posterior tibial pulses on the same side. Therefore, whenever this combination is found a serious attempt should be made to rule out other diseases of the peripheral vascular system. Recently 2 patients suffering from Buerger's disease were evacuated to this hospital with a diagnosis of trench foot. These patients, however, demonstrated an absence of both the dorsalis pedis and posterior tibial pulsations on one side, and it was this observation which eventually lead to the correct diagnosis. Trench foot may for obvious reasons, aggravate and precipitate any latent occlusive disease of the arteries. Furthermore, a patient with a deficient circulation of the foot is more susceptible to trench foot. The combination of trench foot with other organic diseases of the peripheral vascular system has been encountered in several patients of this hospital. The realization that in the vast majority of patients convalescing from trench foot there is no disturbance in the pulse of the foot, in a negative way at least, is of some value in differential diagnosis.

Summary. 1. The incidence of palpable dorsalis pedis and posterior tibial pulsations in 500 soldiers convalescing from trench foot was compared with 906 infantry soldiers without circulatory complaints of the extremities. No significant difference was found.

2. Trench foot is essentially a disease involving the smaller arterioles and capillaries and only in rare instances are the larger arteries involved to the point of occlusion.

3. In a patient convalescing from trench foot an absence of both the posterior tibial and dorsalis pedis pulses on the same side should invite careful search for some other peripheral vascular problem.

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BASAL METABOLISM IN CHILDHOOD: CURRENT PROGRESS

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The resting child releases more heat per kilogram of body weight and per square centimeter of body surface than does the adult. The excess above the adult level is greatest in infancy and diminishes more or less regularly until maturity is reached. Can it be that age, height, weight, and body surface—our ordinary standards of reference—are unsound bases for standardization, so that we must look elsewhere for more perfect measures of reference? Does this excess represent a true physiologic difference between adult and child, due to the phenomenon of growth itself? Moreover, no matter what standards are taken, wide ranges of variation are encountered from child to child. Are these variations due to lack of uniformity in the growth impulse *per se*, or to obscure other causes? These problems are of immense practical importance. Until we have the answers (and the multiplicity of studies still in progress indicates that the questions have as yet been only partially answered) we must view childhood basal metabolism as being still, in part, *terra incognita* to the clinician.

This Review summarizes the major contributions on the more controversial aspects of the subject, and the interpretations offered, as expressed in the medical literature of the past 5 years. For a good outline of the clinical knowledge already at hand the reader is referred to the chapter on basal metabolism in childhood by Talbot[29c] in Brennemann-McQuarrie's "Practice of Pediatrics." The monograph of Du Bois[11] and the various papers by Lewis and associates[19–22] contain critical summaries of the studies on basal metabolism in childhood up to the dates of publication of these individual reports.

Vogelius[31] too has furnished a running survey of the published reports on metabolism standards for children, his last citations being in 1939.

Definition. The basal metabolism is the energy released by the living body when in absolute rest. This energy is released almost entirely in the form of heat.

The body surface area is of the greatest importance in determining the rate at which heat is lost from the warm-blooded human body. Among adults it serves excellently as a method of reference for eliminating the effect of differences in body size upon basal heat output, and most adult standards are expressed in terms of surface area. In childhood, however, as stated in the introduction, the variations are much wider, no matter whether the individuals are compared according to surface area or weight, height, age, or combinations of factors.

The heat production of any given individual at any one time is conditioned by fluctuant influences such as antecedent intake of food, physical activities, and the body temperature. To eliminate these variables the readings are customarily taken at least 12 hours after a meal when the digestive processes are quiescent, with the subject relaxed and free from mental, emotional, and physical effort, and without fever or chilling. The heat output is then considered a measure of the vegetative body functions only. Ideally the subject should be asleep, since the rate is a little lower than when awake (see below) but inasmuch as most people are not able to sleep during the test the heat output in the awake but resting state is taken by common consent as the definitive datum. Every laboratory should try to standardize its performance of the determinations, so that whatever small errors may creep in will tend to be always in the same direction. From the standpoint of the preliminary rest period, it has been demonstrated once more by Nolan,[25] Robertson,[26] and Vogelius[31] that there is no difference between readings from subjects who have walked to a hospital in the morning before breakfast, and when the same subjects have slept overnight at the hospital and remained in bed until tested.

Methods. Measurement of heat production by direct calorimetry required elaborate physiologic apparatus and skilled technical accuracy. For this reason indirect calorimetry is almost universally employed for such measurements. Indirect calorimetry rests on the discovery that a number of body functions such as oxygen consumption and carbon dioxide elimination run parallel, under standardized controlled conditions, to heat production. This has been well validated by comparisons with direct calorimetry. Since the oxygen consumption is the easiest to follow, clinical practice usually utilizes respiration devices which measure the amount of oxygen consumed by the patient in a given unit of time.

A survey of the operational principles and historical development of the modern apparatuses for measuring oxygen consumption has been presented by Roth and Roth.[27] The respiration device most widely used is of the closed circuit type, which employs a gas system linked to the subject's respiratory system, and not connected with the outside atmosphere during the period of the test. The observed rates of oxygen absorption through the lungs and into the blood portray the true rates of intracellular oxidation and therefore of heat production. Roth and Roth conclude that when properly employed such closed circuit devices are dependable and accurate. The reliability of the results depend almost exclusively upon the circumstances under which the tests are done and the coöperation and handling of the subjects. A good exposition of the technical and psychologic aspects of metabolism testing has been prepared by Lex.[23]

Lewis, Iliff and Duval[20] made a direct comparison of an open circuit and a closed circuit method. In the open circuit method the child was placed in a sealed windowed chamber into which outside air could be piped; from the content of oxygen and carbon dioxide in the ingoing and outgoing air the respiratory quotient and the heat production was computed. These workers obtained comparable values for basal metabolism when both procedures were used in close succession with the same child on the same day. They found also that the basal metabolism was not affected by altitude, at least for elevations up to 9000 feet.

Observations. *Sleep.* Sleep does tend to give lowered readings. The studies of Wang and Kern,[32] for example, demonstrated that sleep lowered the metabolism, by as much as 5.7 to 30.6%, with an average of 15%. Lewis, Kinsman and Iliff[22] have summarized the many reported studies which seem to establish this principle beyond question. One criticism which has been repeatedly levelled against Talbot's[29b] standards is that they are a little

low because they include figures from Benedict and Talbot's[2] original investigation in which the determinations were made on sleeping children, and the lowest obtained values were taken for the standards.

Is preliminary training of the subject necessary? Several workers[6,12] have contended that for clinical use the standards of basal metabolism should be based solely on the first test which appears satisfactory, for the reason that this is the one customarily used in clinical practice. Lewis, Duval and Iliff[19c] are the most recent of many workers to take issue with this view. They contend that the first test often gives higher readings due to emotional and other causes, and furthermore that many patients are frequently subjected to repeated tests as the attending physician follows the results of treatment. To check this question by actual experience, these authors reviewed the records of their studies on children aged 2 to 10 years. Of 94 subjects, only 35% gave satisfactory results with the first test; 55% by the second test; 80% by the third test. No determination was considered satisfactory from the standpoint of coöperation unless the child refrained from muscular activity and was relaxed but awake. Once the procedure was going smoothly, however, the results of subsequent satisfactory tests did not differ significantly from the results of the first satisfactory test.

Vogelius[31] likewise found, with girls 7 to 15 years of age, that the oxygen consumption often diminished as the number of determinations was increased. He recommended therefore that enough serial determinations be done until 4 consecutive readings are obtained which no longer show any falling tendency. His average readings for the first determination were 8% higher than the final ones secured by the method recommended. Some of the first determinations were 30% higher than those made later.

Shock[28a] had similarly concluded, from his study of 100 adolescent boys and girls, that "the reliability of metabolism measurements is not significantly altered by repeated testing, provided a preliminary training is given."

Infants. It is in the 1st year of life that the rate of body growth is at its highest. Several recent studies throw a little more light on the metabolism in this period of rapid development. Clagett and Hathaway[9] described repeated observations of 8 infants over a 5 to 10 month period. Six of the 8 children were twins. The open-circuit metabolism chamber method was used and the rates were measured during sleep. Comparison of the figures for twins and non-twins showed no greater similarity for the rates of the twins. The 24 hour output of calories of each infant tended to increase with growth at a relatively uniform rate, yet when the total caloric output was plotted against the separate factors of age, weight, height and surface area, wide spontaneous fluctuations became manifest. The dispersion was least when total calories were referred to age. This was not in accord with the earlier results of other workers, *e. g.*, Levine and Marples[18] who had suggested that stature was probably the best standard of reference for prediction of the infant's basal rate. No sex differences were noted in Clagett and Hathaway's[9] series, and this had also been the experience of Levine and Marples. The conclusion drawn by the authors was that no single basis of comparison is uniformly satisfactory for predicting the basal rate.

Another investigation of what goes on in the infancy period has been reported by Benjamin and Weech.[4] These authors measured the heat output of 4 infants, 2 for as long as 14 months, using an open-circuit metabolism chamber and performing the estimates 1 to 3 times weekly. The average daily fluctuation ranged from 6 to 14%; the coefficient of variation for 257 observations of the 4 infants came to over 9%. In general younger infants showed larger fluctuations than those who were older. These estimates of longitudinal variability were compared with

the scatter exhibited by cross-sectional analyses of heat production in infancy as studied by other authors.[2,18] The latter had an even higher coefficient of variation, namely 14.9%. Such variability renders it difficult to establish reliable correlations between heat production and measures of growth when the period of observations are short.

Benjamin and Weech next related heat production to different measures of growth to see which would have the highest correlation. They noted first of all that such correlations are hampered by the spontaneous erratic fluctuations of the individual children. The association between total calories and body weight was closest, without any significant change over the age period studied. The associations between total calories and both surface area and height were less marked, but with some direct relationship. The authors concluded that, while a trend to reduction in the caloric output per kilogram of body weight may proceed at a slow and almost uniform rate through infancy and childhood, the rate of this decline does not manifest an obvious relationship to the rapid changes in the rate of growth which take place during infancy.

They encountered no "kink" in the individual energy curves at the end of the 1st year of life, as has been theorized by some workers[34b] on the basis of mean statistics derived from cross-sectional studies. They pointed out that metabolically active organs have higher rates of heat production than those less active; that the total heat given off by the body is the sum of all the individual fractions of heat derived from the separate organs and tissues; and that as the relative weights of the organs alter with advance in age the total heat production becomes correspondingly modified in a way not exactly proportional to increase in total body mass.

Children of Preschood Age. Lamb[16] was able to train 8 children 2 to 4 years of age how to relax completely while being tested with the conventional mask and closed-circuit oxygen method. She determined the basal metabolism of these children at 3 month intervals for 1 year, and compared the results with the few tables of standards already available. The subjects were healthy, 3 girls and 5 boys, attending a nursery school. Two tests were made on each morning, and repeated on successive mornings until the lowest figures obtained for calories per hour agreed within 5%. To meet this criterion, 4 to 6 tests had to be made with every child. In nearly half the tests all 4 recordings made on 2 different mornings with each subject checked within 5% of the lowest value.

The crude figures for calory utilization showed wide variations. From the calories per hour the authors computed the calories per square meter of body surface, the calories per kilogram of body weight and the calories per centimeter of height. With every child the smallest spread of the figures occurred when metabolism was expressed as calories per square meter of surface area, the maximum being about 20% above the minimum value. For calories per centimeter and per kilogram the maximums were respectively 23 and 25% above the minimums.

The data were compared with 4 sets of standards recommended for children (Benedict,[3] height; Dreyer, height; Talbot,[29] height and weight). The extremes ranged from +31% with 1 boy with the Talbot weight standard to −20.1% with another boy with the Dreyer standard. The greatest differences were between the Benedict height and the Dreyer standard. Dreyer's was the only formula for a standard which gave a consistently negative deviation. The author commented that these discrepancies emphasize the need for more accurate standard for children. Other reports on basal metabolism of healthy normal children, in this age period also show negative deviations from the formula of Dreyer and positive deviations from the standards developed by Benedict and Talbot.

In conclusion Lamb suggested that probably various stages of maturation

exist in children of the same chronologic age, and that basal metabolism is related to the rate and extent of maturation. Basal metabolism values for children therefore cannot be compared successfully on the basis of chronologic age alone; the basis must allow also for the developmental progress. Standards must incorporate such allowances.

Childhood Period. The results of careful studies on basal metabolism in children between 2 and 12 years of age in Denver were summarized in 1937 by Lewis, Kinsman and Iliff[22] and again in 1943 by Lewis, Duval and Iliff[19a,b] in carefully documented reports.

The children studied by Lewis, Kinsman and Iliff were normal. There were 718 satisfactory tests of 57 girls and 1007 satisfactory tests of 70 boys. They were between 2 and 12 years of age when tested. The determinations were made by the open circuit chamber method. The data for the boys and the girls were tabulated separately, and then the caloric outputs per hour were computed according to the body characteristics of age, weight, height and body surface, and also for the other characteristics as related to age. The scatter about the means for all of these bases of computation was about the same, except that height showed a greater dispersion. From meticulous comparisons of their data with the figures from other sources they conclude that the range of normal variation may extend approximately ±17% from their own values. Reported values lower than this range of variation may be explained by the subjects having been asleep during the tests, and higher results may have been due to different experimental conditions. They concluded that when the caloric output per hour is calculated for any single subject by the different methods of referring the heat production, the figures obtained will vary from the normal to approximately the same degree regardless of the method, *provided* the height and weight of the child, and hence his body surface, are close to the means for normal children in his age group. In other words, with well-proportioned children the physician may use any one of the three sets of central trend line values which showed the lowest coefficients of variation: calories per hour per square meter referred to age, calories per hour referred to weight, or calories per hour referred to body surface. On the other hand, with children whose measurements fall outside the range of the children who were used as subjects for the standards, the rates obtained by the different methods of referring the metabolism may differ considerably one from another. A further collection of data is needed, with a comparative study of the anthropometric measurements and basal metabolism findings. Until such a correlated study has been made the authors recommend that all three sets of the standards mentioned above be given consideration in judging the status of such patients.

In their reports the standards are presented according to calories per hour per square meter referred to age, and calories per hour referred to surface area, weight, and height, respectively, because dispersion was least with these methods of reference. Calories per hour in terms of height had a somewhat high variation, but the values are included because this method of reference has been widely used by other workers. Their paper contains, in addition, graphs which compare their standards with those of recognized authorities in the field, such as de Bruin,[10] Talbot,[20a,b] Bierring,[5] Boothby, Berkson and Dunn,[6] Miana-Calabrese,[24] and Webster, Harrington and Wright.[33] The trends for all are much the same, though the values from these various studies do not coincide precisely.

The standards are given as average or mean values. The authors have calculated the various coefficients of variation: 95% of their healthy children fell within ±12% of the standards when calories per hour were referred to weight or surface area, and when calories per hour per square meter were referred to age; 99.7% of nor-

mal children fell within ±18% of these standards.

Adolescence. Among the older authorities there is considerable disagreement over whether a positive increase in the relative heat production takes place at the time of puberty. Göttche,[13] Lax and Petényi,[17] Topper and Mulier,[30] and Kestner and Knipping,[15] for example, have described a rise, whereas Boothby and Sandiford,[7] Bailey,[1] and Bierring[5] failed to substantiate it. All of these workers employed the method of group sampling at different age periods. Webster, Harrington and Wright[33] in 1941 attacked the problem from a different aspect, reporting on longitudinal observations of one group of children over a 6 year period. They measured at approximately 4 month intervals the basal metabolism of 13 boys and 8 girls in rural New York state, commencing at age 10. The closed-circuit method was employed and the reports were expressed in terms of surface area. In the period of preliminary training nearly all the children displayed a sharp decrease in readings. From then on, however, only rarely was there a striking variation between one observation and the next. With both the boys and the girls the deviations of the individual readings from the mean curves were not marked.

In accord with the experience of all previous observers the basal metabolism for the boys was higher than that for the girls. There was a gradual decline in the basal metabolism (calories per square meter of body surface per hour) over the age period 10 to 16 years for both boys and girls. This was most striking between ages 11 and 12 years. The closest conformity was with the Bierring standards for boys and the Kestner and Knipping standards for girls. The onset of menses produced no significant change in heat production. For the boys the total output of calories per 24 hours rose progressively over the entire period, parallel with growth in height and weight. For the girls this was true until the mean age of 14½ years, above which the rate of increase in total calories became much less marked. This coincided with a fall in the body weight curve and a flattening of the curve for increase in height.

Lewis, Duval and Iliff[19a,b] have also presented some figures on normal children 13 to 15 years old, inclusive. In general, the lowest degrees of scatter were encountered when the results were expressed in terms of the same characteristics they found most satisfactory for younger children. (See discussion in preceding section.) A detailed comparison is given between their mean values and similar data reported by other workers. Many of the other reported standards fall within ±5% of the mean values of this study. The authors comment that no explanation is at hand for the relatively high values for adolescent girls reported by Topper and Mulier.[30]

Shock[28a] carefully carried out repeated measurements of basal metabolism by the Tissot open-circuit technique on a group of 50 adolescent boys and 50 adolescent girls. He was desirous of determining which measure of growth could serve as a basis of reference, and attacked the problem by noting which of the body properties for normal subjects of a given sex and age gave the smallest range of values in the readings. Determinations were made in triplicate on each of 2 successive days every 6 months over the age interval 11.5 to 18 years. Calculated for both boys and girls at each age level were the coefficients of variation for (*a*) calories per square meter per hour, (*b*) calories per kilogram per hour, (*c*) cubic centimeters of oxygen consumed per square meter per minute, (*d*) cubic centimeters of oxygen consumed per minute and (*e*) total cubic centimeters of oxygen per kilogram per minute. Coefficients of variation were consistently lower for calories per square meter per hour and for cubic centimeters of oxygen consumed per square meter per minute than for similar values expressed per kilogram of body weight. His results, therefore, were expressed in terms of cubic centimeters of oxygen consumed per square

meter per minute and of calories of heat produced per square meter per hour.

Shock compared his data with other reports and found, strikingly, that the differences in average metabolism values in reports of different observers were greater than the average age trends shown during adolescence in any single study. "It seems that careful standardization of techniques is as important in the interpretation of the results of metabolism tests as is the question of the chronologic age of the subjects."

Shock's analysis brought to light also that the range of values for basal metabolism which will include 95% of a normal population at any given age between 11.5 and 17.5 years is greater than the average change in metabolism with growth over the adolescent period. A deviation of ±15% from the mean will include approximately 95% of normal children but a deviation of ±20% from the mean value is necessary to include 99% of them within this age range. The conventional limits for normalcy of ±10% deviation from the mean value are, therefore, too narrow; they should be extended to at least ±15% if norms expressed in terms of chronologic age are to be used.

The question of the effect of menarche on basal metabolism of adolescent girls was also reëxplored by Shock,[28b] who determined the basal metabolism of 50 California girls at 6 months intervals, starting at age 11 and continuing for 6 years. Careful notes of the menstrual phenomena were coincidentally made. He tabulated the respective ages as months before or after menarche, instead of as chronologic age. The basal oxygen consumptions were calculated in relation to surface area, which in turn was computed from height and weight. It was found that a sudden rapid fall in basal oxygen consumption took place with the beginning of menstruation, or 6 to 12 months earlier. The mean curve which was approximately 41 calories per square meter per hour up to menarche had fallen to approximately 35 calories per square meter per hour 24 months later, and then continued to fall, but more slowly, until the full adult level was reached. The phenomenon was interpreted as another aspect of maturity, rather than a consequence of endocrine changes associated with menstruation. With reference to the possible existence of a prepubertal rise in basal oxygen consumption the author commented that his observations did not begin at an early enough chronologic age to answer that question with assurance, though many of the individual girls, especially those who menstruated late, seemed to have such a prepubertal rise.

Johnston[14] described observations of basal metabolism and calcium and nitrogen balance in 6 tubercular adolescent girls studied over 9 day periods for 300 continuous days. In these girls sexual maturation was accompanied by a decrease in the calcium and nitrogen retentions. There was first a physiologic rise in basal metabolism, followed by a fall at about the menarche. Johnston suggested that the metabolic retentions paralleled the metabolic rate, apparently as a phenomenon of growth. He cited several other girls in whom the premenarcheal rise in basal metabolism was accompanied by toxic manifestations of hyperthyroidism. These girls were given iodine therapy and rest in bed, and a prompt fall in the metabolic rate occurred at the onset of the menses. He recommended that small doses of desiccated thyroid be given if the depressed phase of the metabolism cycle should reach a pathologically low level.

Vogelius[31] was interested in exploring more adequately than hitherto achieved the problems involved in setting up basal metabolism standards for girls aged 7 to 15 years. He accordingly analyzed 1150 tests with 150 normal Danish girls, and a smaller number of tests with children obese, dwarfed, or suffering from other disorders of metabolism. He also reviewed critically the reports from other workers, notably that of Bierring[5] on Danish boys.

When doing the basal metabolism tests the following data were obtained for each

subject: age, oxygen consumption, weight, height, and surface area computed according to Du Bois' "linear formula." He made a careful statistical investigation of these various data, utilizing a new mathematical approach—that of "stepwise confluence analysis." If the observations were divided into two age ranges, namely 7 to 15 years and 16 to 18 years, the exact age within these ranges could be ignored. Basal metabolism seemed best characterized by formulas built up to include oxygen consumption, surface area, weight and height. Inasmuch as these computations are highly involved, one can get along on a simpler basis using weight as the basis of reference, provided the girls are normal with respect to weight-height ratio. The author provides 2 monographs for the evaluation of the ratios of metabolism-weight and weight-height. He provides also a table of metabolism standards for girls aged 7 to 15 years, in which the data are given as calories per 24 hours for body weights from 15 to 75 kg. The table gives not only standard values but also the lower and upper 95% limits. These standards do not fit subjects who may be obese, dwarfed, or otherwise abnormal in the height-weight ratios given.

Vogelius is highly critical of the common practice of expressing the metabolism in terms of per unit of weight or per unit of surface area in relation to age. For one thing, each of these variables already reflects growth changes due to age over the years up to age 16. For another, as illustrated by examples from data of other workers, differences in weight or surface area become carried over with undue emphasis into the final results. Furthermore, the problem of comparison of standards is not solved, since no pair of standards proposed by different workers run exactly parallel. Clearly the information at hand for evaluation of all the factors which determine the basal metabolism is not wholly complete.

Brown and Wasson[8] reported 154 tests of basal metabolism performed on 97 ambulant children ill with rheumatic fever. They used the closed circuit method and derived their calculations from the height-weight (or surface area) standard of Boothby and Sandiford.[4] The age distribution of the children was not reported, and there is no statement whether preliminary training was given. The mean of the rates was 7.6%. Forty-three children had at least 1 reading below 10%. Of 33 children who had more than 1 test, 21 gave lower readings in the second tests which were performed during the spring.

Diagnosis of Hypothyroidism. Wilkins and Fleischmann[35] judge the determination of the basal metabolic rate to be of little aid in diagnosing hypothyroidism in childhood. They found that slight emotional disturbances can accelerate the rate for long periods, and this may not be detected by the observer. Younger children and mentally defective children usually do not coöperate well. In fact in only 1 of every 4 children with hypothyroidism studied by Wilkins, Fleischmann and Block[36] could satisfactory determinations be obtained. Furthermore, even when the performance of the tests is satisfactory, the selection of a proper standard for comparison becomes difficult. If the hypothyroid child is dwarfed, inadequate standards are available; if he is obese the low oxygen consumption of adipose tissue gives rise to abnormally low figures when referred to surface area standards. With the surface area standards the results of tests of obese children with no signs of hypothyroidism may be as low as −25 to −40%. With the Talbot height standards obese children without hypothyroidism usually have rates which are normal or even elevated, whereas hypothyroid children have rates which are low. Yet occasional children have been seen whose rates have been low with the height standards but without signs or symptoms of thyroid deficiency. To avoid error, therefore, the diagnosis of hypothyroidism must not be made on the basis of a low metabolic rate alone. Other abnormalities such as sluggishness and hypercholesterolemia must be associated.

Influence of Growth. Wetzel[34] has emphasized that growth in the biologic world seems to follow certain well-established dynamic principles which are expressible in mathematical terms. Complex equations may be derived which can be applied equally to the phenomenon of growth as it is operative in tadpole tails, yeast cultures, tissue cultures, oxygen consumption of the fertilized egg of Echinus and heat production of the chick embryo. Human basal heat production as measured by authorities such as Benedict and Talbot[2] can also be shown to conform rather closely to these theoretical trends. Growth is an integral part of these equations, and is one element in determining the heat production and oxygen consumption of the human child. However, within the span of relatively short periods of time, such as 1 or 2 years, the changes in the metabolism due to changes in intensity of the growth impulse are much smaller than the variability of the individual measurements, and for that reason escape detection.

Wetzel has devised an intricate growth chart, known as a "grid," for portraying and appraising the growth and development of children. With this chart one first plots weight against height to obtain the "development level," and then plots this value against age to ascertain the "schedule of development." For a full exposition the reader is referred to the original presentations.[34] The grid chart contains a scale for estimating basal metabolism of boys and girls directly from the horizontal extensions of the level lines without further correction for "off-size," age, or body build. The exact manner in which this scale of basal metabolism values has been built up is not obvious from the text. When evaluating the basal metabolism of any child, one measures the heat production in the usual manner and then compares it with the printed estimate of what a normal child's metabolism of the same height and weight should be. When the measurements are carefully done and sufficiently repeated, "observed values in children otherwise known to be healthy will frequently not differ from the grid standards by more than ±7%." The factors of age and physique do not need to be considered, according to this author, because growth, and not chronologic age, is the conditioning factor. He argues further that not all of a subject's height and weight is involved in heat output but only "that portion of each of these 2 measures of size which, in combination with the other, yields the component of development." The technique is said to work equally well with obese children inasmuch as the factor of physique is not incorporated into the calculations.

The recognized authorities in the field concede that Wetzel's approach to the relationship between growth and metabolism may be original and provocative, and helpful with many individual cases. They feel, however, that this approach is not yet the complete answer to the problems of just how the influence of growth upon metabolism can be measured and why so wide a range of basal readings is met with among children who appear to be similar with regard to the various measures of growth.

Summary. Many tables for the resting oxygen consumption of normal children have been gathered to serve for the evaluation of the status of other individual children. These standards are expressed customarily in terms of units of age, or height, or weight, or surface area, or of several of these growth measures in combination. Age is the least satisfactory as a direct basis of reference. There is no universal agreement as to whether height, or weight, or surface area, with or without reference to age, work out the best in actual practice.

With children of average or normal body build any of the different types of standards seems to work well. But when the body build is atypical or distorted, as, for example, with obese children or dwarfs, the different standards give results which fail to conform one with another.

The normal range for individual varia-

tion is greater in childhood than in adult life. One reason for this appears to be the growth impulse, which stimulates the metabolism to an as yet unmeasured degree. Obviously, we must work out more fully the importance of growth, and of the thyroid gland, and of other controlling factors now only guessed at. Until then the physiologic significance of basal metabolism measurements in childhood must remain obscure and of little clinical value in the presence of prominent deviations from the patterns of most normal children.

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GYNECOLOGY AND OBSTETRICS

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PUERPERAL INFECTION

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Puerperal infection is referred to as puerperal fever, puerperal sepsis, and childbed fever.

Historical. Excellent descriptions of cases of puerperal infection were written by Hippocrates (400 B.C.) and other early writers and references to it throughout the Middle Ages are numerous.[17] It was not until the advent of hospitals in the 17th century, however, that the disease became epidemic in nature. During this period when nothing was known about contagion, extremely high mortalities resulted from puerperal infection. White[76] (1773), and Gordon[26] (1795) did much to help establish the principles of cleanliness, disinfection and segregation. Holmes[36] in 1843 published his famous paper "The Contagiousness of Puerperal Fever," in which he proved that the disease was transmitted directly or indirectly from 1 individual to another. Semmelweis[66] (1847) showed unequivocally that puerperal fever is an infection of the genital tract and indicated the correct manner of its prevention. In 1879 Pasteur[59] demonstrated the presence of streptococci in the blood of a puerperal sepsis patient both before and after her death. From that date every form of puerperal sepsis was attributed to this agent, until later research clearly demonstrated that there is no specific organism for puerperal infection.

Source of Infection. Puerperal infection arises from the genital tract and is most frequently acquired just before, during, or soon after delivery. Parturition causes many wounds in the birth canal that may serve as portals of entry for microörganisms; but the chief factor in the etiology of puerperal infection is the carrier who directly or indirectly transmits virulent bacteria to the birth passages.

Infectious spray from the nose or throat of those in attendance is a well-established source of contamination.[12,51,58,67,73] Williams[77] has shown definitely that the curve of the incidence of puerperal infection follows the curve of the incidence of respiratory infection, but at a somewhat later date Smith[67] and Colebrook[12] have shown that the parturient can be infected by secretions of her own mouth and nose. Fingering of the vulva and vagina by the patient before, during and after labor is a source of infection. Horn,[37] Von Buben,[7] and Liubimowa[45] have emphasized the danger of infection following coitus before or early in labor. Vaginal douches before, during or after labor have been associated with puerperal infection. Any break in aseptic technique in spontaneous or instrumental delivery, catheterization and postpartum care of the vulva, and inadequate sterilization of a common bed-pan and other sick-room accessories are all sources of contamination.[4]

Many investigators[46,69,78] have studied the bacterial content of the vagina and cervix, and a multitude of various microorganisms have been cultured from the

cervix during pregnancy and many conclusions have been reached. Some of these organisms are morphologically and culturally identical with bacteria which initiate pathologic changes, although the incidence of such organisms varies greatly in the reports of different observers. In Conti's[15] study (1941), streptococci were obtained in cultures from 14.5% of his patients, and in 3.3% the bacteria were hemolytic. He found that morbidity was somewhat higher in patients in whom the cervices harbored streptococci, especially if these organisms promote hemolysis. He believes endogenous infection from the cervix does occur, but in his series was exceedingly mild and of short duration. Bumm and Sigwart[9] concluded from their study that there was no definite relationship between streptococci cultured from cervices during the antepartum period and puerperal morbidity. Douglas and Davis's[20] study of 1000 patients indicates that the great majority of infections occurring during the puerperium and postabortal period were endogenous in origin, and caused for the most part by different groups of non-hemolytic streptococci. The organisms they considered exogenous in origin were the hemolytic streptococcus, *Staph. aureus*, pneumococcus, and other pyogenic organisms not usually found in the cervix or vagina. These, they believe, were brought to the genital tract by the patient or her attendants. The second group of exogenous organisms included the gram-positive bacilli, *Cl. welchii*, and some strains of streptococci whose normal habitat is in the gastro-intestinal tract. These organisms, they believe, were introduced into the genital tract during various diagnostic and therapeutic procedures. Williams[78] states that while bacteriologic research affords a certain amount of evidence of autoinfection, clinical observation speaks against it. Kulka[43] found that a bacteremia existed in 18% of women during normal afebrile labors and puerperia. The organisms usually found in the blood were the colon bacillus, the *Strep. hemolyticus* and staphylococci. On the 3rd day after delivery, all blood cultures were negative in his study.

BACTERIOLOGY. One of the most valuable additions to our knowledge of puerperal infections during recent years is a more exact appreciation of its bacteriology and morbid anatomy. Modern serologic techniques have resulted in the separation of various bacterial species into groups, types and sub-types which are of great value in making an adequate diagnosis. Unfortunately, even with present-day knowledge of serologic type at their disposal, the bacteriologists cannot sort out and segregate the "dangerous carriers" by the nature of the microörganism they harbor.[2]

The organisms most often identified in the severe and fatal infections are the hemolytic streptococcus, the anaërobic streptococcus, *Staph. aureus* and *Clostridium welchii*.[34] Also, *Strep. pyogenes*, *Staph. citreus* and *albus*, *Neisseria gonorrhœæ*, *Diplococcus pneumoniæ*, *B. coli*, *B. diphtheriæ*, *B. pyocyaneus* have been asserted to be causative factors. The common pyogenic organisms are most frequently responsible. *Strep. pyogenes*, hemolytic and non-hemolytic, as well as anaërobic and aërobic streptococci are the commonest invaders, and have been shown to be present in the uterus, or in the blood stream, in about 75% of all infected patients.[30,64] All known organisms, both pathogenic and non-pathogenic, have been identified with the disease. The virulence of the organism responsible for the infection seems important. Present-day knowledge of "virulence" in most cases is but little advanced from that of Weigert,[75] who in 1875 asked whether the "something" that renders a microörganism virulent is a vital bacterial product of merely "something" attached to the microörganism. Goodall[25] states that virulence as a property of microbes is a more or less fixed quantity, and that virulence varies in each infected patient with the natural resistance or lack of resistance of the individual.

The frequent demonstration of strepto-

cocci and staphylococci in the genital secretions gave rise to the assumption by Koller,[42] that the mere presence of these organisms was not sufficient to explain the pathogenesis of puerperal infection. When the virulence of the bacteria of the genital secretions was determined, it was found that after spontaneous deliveries the incidence of temperature increases was not higher in the patients in whom the virulence of the bacteria was high than in those in which it was low. However, after operative terminations of birth in the presence of virulent vaginal bacteria, the inflammatory complications were frequent and prolonged. Watson[74] presents data suggesting that there are 2 main types of puerperal infection, 1 caused by a virulent strain of an aërobic hemolytic streptococcus and the other by an anaërobic streptococcus.

Bacterial synergism may account for some cases of severe puerperal infection. It has been demonstrated by Steinhorn[69] that the virulence of anaërobic streptococci is markedly increased by their association with a strain of *Staph. albus*, so that such mixtures are highly invasive for white mice. Weinberg and later Morosova[54] have called attention to the fact that when an anaërobic infection (*B. welchii*) even of the slightest degree, is associated with *B. coli* infection, the virulence of the anaërobic organism is greatly increased. Colebrook and Hare[10] present data to suggest that there are, in all probability, several distinct types of anaërobic streptococci.

Morbid Anatomy. Puerperal infection begins as a local septic infection in the soft tissues of the birth canal. The resulting inflammatory process may remain local, or may extend by metastasis to other parts of the body. Local lesions may be limited to any structure in the birth canal or may involve the entire birth passages and the adjacent tissues of the parametria and peritoneum.[4]

Tears in the vulva and vagina, when infected, may react as do similarly infected wounds in other parts of the body. The surrounding tissues are swollen, red and painful, and there is usually a purulent and foul smelling discharge.

When the uterus is infected, the condition is known as endometritis. In mild cases where the infection is believed limited to the basal layer of the decidua, it is often spoken of as deciduitis. The severity of the uterine infection varies with the type and virulence of the invading bacteria, and the adequacy of the maternal defensive mechanism. The less virulent organisms tend to remain confined to the endometrium and produce an area of necrosis and decidual débris. A more virulent organism or a diminished defensive reaction may lead to a rapid invasion of the blood stream, or lymphatic extension to the myometrium, parametrium and peritoneum, without much alteration in the endometrium.

An infection of the myometrium may or may not precede or accompany parametritis. A protective wall of leukocytes[8] beneath the endometrium usually protects the uterine musculature from direct invasion, but at times this may prove inadequate to prevent local abscess formation.[63]

Infection that spreads through the lymphatics beyond the uterus may be checked in the pelvic cellular tissue. In this event, a pelvic cellulitis develops. The tissues of the parametria become swollen by a serous effusion. This may remain as a gradually subsiding cellulitis which resolves by itself; it may develop into a hard induration extending to the lateral pelvic walls which may last for months; or it may become localized into an abscess cavity, which may extend outward to the wall of the pelvis and then upward between the peritoneum and the abdominal wall in the region of Poupart's ligament, or it may follow the course of the uterine vessels to the pelvic brim and point above the crest of the ilium.

Extension of the infection through the lymphatics to the peritoneum may take place early or late in the course of a puerperal infection, and when it does occur, it is more frequently the last step in the

sequence of events which includes endometritis and parametritis. When the peritoneum is invaded, Nature attempts to wall off the infection and limit it to the pelvis by the formation of adhesions between the sigmoid, cecum, bladder and omentum. General peritonitis results if this effort is not successful.

The tubes and ovaries may participate in an extensive puerperal infection, or a perisalpingitis and perioöphoritis may follow in the course of a pelvic peritonitis.

If the thrombi which are normally present in the uterine sinuses following delivery become infected, the surrounding vessel walls show evidence of phlebitis. As these thrombi disintegrate new thrombi are formed, and extension of the inflammatory process continues in the vessel walls. If the thrombophlebitis is limited to the uterine wall, the inflammatory process may subside or local abscess formation may occur. The process may extend outside the uterus to the iliac and femoral veins.

Thrombophlebitis may lead to metastatic lesions, the most frequent of which are found in the lungs, and give rise to many complications of that organ. Bacterial emboli may pass through the lungs and cause acute endocarditis and other distant inflammatory lesions.

If the infection is gonorrheal in origin, it usually extends to the uterus from a previously quiescent infection of the cervix or lower birth passages. It advances by continuity along the surface of the structures involved and results in a typical gonococcal salpingitis. Mengert[52] emphasizes the slow growth of the gonococcus and the delayed involvement of the Fallopian tubes. A local pelvic peritonitis may result from the discharge of purulent material from the tubal lumina.

Diagnosis. Any postpartum patient with a temperature rise of 100.4° F. on any 2 days, exclusive of the 1st 24 hours, is considered morbid, and her fever is considered to be pelvic in origin until proven otherwise. It should be kept in mind that other infectious processes may coëxist with a genital infection, and that the organism may be the same in both processes. A sustained temperature curve without the usual morning remissions indicates a widespread infection.

The pulse rate is an excellent indicator of the course of the disease, especially when the temperature begins to be brought under control. It should be evaluated in the light of hemorrhage and recent hemoglobin and hematocrit readings.

The patient's reaction to infection will vary with the site of infection, and with the virulence of the organism. As a rule, the systemic reaction is slight with vulvar, vaginal and minimal decidual infections, as long as drainage is good. With the spread of infection the patient's feeling of well-being leaves her, and she may complain of headache, loss of appetite, fatigue, sleeplessness and chilliness. Tenderness and pain in the pelvis are often early reliable symptoms of beginning invasion of the parametria. The gravity of the patient's condition is indicated by the degree of temperature, the character and rate of the pulse and respiration, the change in the leukocyte and red blood cell count, and blood and cervical culture.

Abdominal examination may reveal an enlarged, soft, and tender uterus which usually is present in cases of endometritis. When pressure on the abdomen causes pain, and rebound pain is elicited, one should consider peritonitis a definite possibility. Rectal examination may reveal a hard, unyielding, sensitive induration of the parametria which may extend out from the uterus on one or both sides to the pelvic walls. This induration restricts the mobility of the cervix.

Inspection of the vulva often will reveal the presence of infected perineal lacerations or episiotomy wounds.

Vaginal examinations are generally contraindicated in that they may be followed by extension of the infection. However, when there is good reason to believe that further information must be obtained, vaginal examination should be done with

great gentleness and under aseptic precautions. The examination should be limited to determining whether or not there is a mass in the broad ligaments and whether or not that mass is fluctuant.

As to differential diagnosis, one must distinguish most frequently between a genital tract infection and pyelitis. We have discarded the idea that a slight rise in temperature the 3rd day postpartum is "milk fever." More likely it is a mild deciduitis. Upper respiratory and throat infections must be kept constantly in mind and the possibility of autoinoculation appreciated. Pneumonia must be considered, especially in those patients who received inhalation anesthesia at delivery. Appendicitis and malaria are seen infrequently in the puerperium.

Prognosis. As long as the inflammatory process is localized to the vulva, vagina, and endometrium the prognosis is favorable. An endometritis with profuse foul lochia is considered a less dangerous infection than when the lochia are less foul and scant. The prognosis becomes less favorable as the infection spreads. Extension to the parametria is serious but usually can be treated successfully. As long as peritonitis is limited to the pelvis ultimate recovery may be expected, but sterility and a prolonged convalescence often follow. Thrombophlebitis may prove fatal. The possibility of pulmonary embolism is always present with thrombophlebitis. General peritonitis and bacteriemia carry a poor prognosis.

Treatment. Since pyogenic bacteria are responsible for puerperal infections, protecting the genital tract from contamination is the most important phase of treatment. The vaginal secretions are protective in nature, and if given sufficient time will render innocuous most bacteria that gain access to the birth canal. To realize the maximum benefit from this natural barrier, vaginal douches and sexual intercourse must be absolutely avoided during the latter months of pregnancy. Showers rather than tub baths should be used.

All foci of infection should be eliminated as early in pregnancy as possible. This is true especially in case of infections of the external genitalia, regardless of how slight they may appear. Vulvovaginitis and gonorrhea should be treated during pregnancy, but cervical erosions and lacerations are probably best treated by being left alone.

The general condition of the patient is becoming ever more important in the prevention and treatment of infection. A diet adequate in proteins, minerals and vitamins,[56] sufficient rest, and outdoor recreation are measures of importance. The correction of anemia during pregnancy is obtained by proper diet, iron, and liver extract. The routine administration of iron is widespread, and there is a growing tendency also to prescribe liver extract during pregnancy.

The problem of developing immunity and of increasing natural resistance have not been solved, and there seems to be very little that one can do in this direction other than to recommend general hygienic measures. Specific immunization has been tried, but its value has not been proved. Adair and Hac[1] immunized over 1100 patients against streptococci, but the postpartum febrile morbidity rate of these patients was not better than the morbidity rate of non-immunized individuals. Bernstein and Otten[5] vaccinated 51 patients with suitable vaccine with a puerperal morbidity of 5.9%. Evidence obtained by Colebrook suggests that antistreptococcus serum may have an unfavorable effect on puerperal infections.[11]

Youth is a great ally in combating infection, and according to Eastman[21] the incidence of puerperal infection is no greater in mothers who have their babies close together (12 to 24 months interval) than in those who have their babies after longer intervals. Whatever advantage is gained by a rest period of several years between births seems to be offset by the factor of increased age.

Labor. It is now well recognized that the safest place to conduct labor from

the point of view of infection is in a well-managed maternity hospital. Stout's[70] study showed the incidence of puerperal infection to be almost twice as great in a series of normal women delivered at home as in a comparable group delivered in the hospital. No difference in the severity of the infection could be detected between the 2 groups.

On entering the labor floor, after being evaluated by a physician, the first thing a patient should receive is an enema which thoroughly empties the bowel. The suprapubic and vulvar regions are shaved, and in many maternity hospitals a shower bath is given if the patient is not clean. The progress of labor should be followed by infrequent rectal examinations, and should a vaginal examination be indicated, it must be preceded by proper preparation of the vulva and the hands of the physician as is done for the actual delivery.

The literature would seem to indicate that the instillation of antiseptic solution into the vagina leads to a lower morbidity rate.[6,50,81] Mercurochrome is employed most frequently but many other substances, including zepherin chloride and acriflavine in glycerin, are also used. Many obstetricians do not consider such treatment necessary, feeling that any invasion of the lower birth canal increases the chances for contamination. Douglas and Davis believe that the logical approach to endogenous infections is the introduction of antiseptic or germicidal agents into the vagina during labor.[20]

Adequate sedative during labor, and especially during prolonged labor, is necessary to avoid exhausting the patient at delivery. There is no one method for the relief of pain and conservation of the patient's energy, but many reliable methods of sedation are well known and widely used.

The high incidence of puerperal morbidity following postpartum hemorrhage is well known.[3,41] Pastore[60] points out that the mismanagement of the third stage of labor is responsible for the majority of these hemorrhages. In the non-bleeding third stage, the management consists largely of watchful waiting until the signs of placental separation are present. After the separation of the placenta, the uterus is massaged until it contracts, then the placenta may be expressed artificially with safety. The uterus should be held for 1 hour by a reliable attendant. Oxytoxic drugs are valuable in preventing and controlling hemorrhage. Posterior pituitary extract has a rapid and vigorous action on the uterus while ergonovine has a rapid and more lasting effect. An ice-bag over the fundus also has an oxytoxic effect.

Laceration of the perineum and vagina should be aseptically repaired immediately. Postpartum care of the vulva should be similar to the case of any open or potentially infected wound. An ample amount of easily digested foods and sufficient fluids to insure 1 liter or more of urinary output are important. The Semi-Fowler position, and having the patient lie on her side and abdomen facilitate drainage. An ice-bag over the uterus has a stimulating and pain-relieving quality. Rest is essential, and is best secured by competent nursing and adequate use of morphine or codeine.

Ergot preparations should be used both because of their effect on uterine tone and their stimulating effect on the reticuloendothelial system.[48,49] Antipyretic drugs and cathartics are generally contraindicated. A low enema and forced fluids are recommended instead.

Connally[14] has found that 5 mg. per day of stilbestrol, administered during the 1st few days of the puerperium, reduced the incidence of morbidity to less than one-third that of a control group of patients not receiving this drug. In patients where lactation is contraindicated or undesired, stilbestrol may be of benefit.

Blood transfusions are of utmost importance in the treatment of puerperal infection.[62] Excessive blood loss during delivery should be replaced prophylactically. All blood should be properly typed and cross-matched. Rh positive blood must

not be given to an Rh negative patient. This is especially true where future pregnancies and repeated transfusions are to be considered. Small transfusions of 250 to 350 cc. may be given daily or less frequently as indicated by the course of the disease. They should be employed early, and before the onset of alarming symptoms and be continued until recovery is certain.

There is no universally recognized treatment of phlebitis, thrombophlebitis and phlebothrombosis during the puerperium. The prophylactic practices of wrapping the legs immediately after delivery of those patients having varicosities, and getting obese women out of bed early in the puerperium are well worth following. Elevation and wrapping of both legs, heat cradle, keeping the patient well hydrated and at rest are the usual conservative methods of therapy. Chemotherapy should be used in the presence of a temperature rise. Mengert's study[53] showing that the uncomplicated obstetric patient stands only 1 chance in almost 35,000 of embolic death from bland thrombosis, emphasizes the importance of guarding against interfering with Nature's efforts. The recent reports advising surgical treatment[65] and anticoagulant therapy[16] must be critically interpreted. Obstetrical patients will probably experience far greater danger from the anesthetic and operation than they will from the disease. The complications of heparin and dicumarol therapy must be kept constantly in mind and the prothrombin level and coagulation time must be carefully followed. Therefore the postpartum patients eligible for these types of therapy must be carefully selected. The use of continuous caudal anesthesia in acute thrombophlebitis, to counteract the tendency of vasoconstriction, may prove itself a worthwhile addition to the management of the disease, but the dangers of this type of anesthesia must be recognized.

Surgical measures are limited to incision and drainage of pelvic abscesses. When a pelvic abscess points in the vaginal cul-de-sac and is fluctuant, it should be drained by colpotomy. If the abscess points on the lateral anterior abdominal wall and fluctuation can be demonstrated, incision and drainage is indicated.

Recovery is the rule in puerperal infection. The majority of all cases which are included under morbidity rates are symptom-free and show only the changes of fever, leukocytosis and elevation of the pulse rate. Any therapeutic measure that interferes with Nature's efforts to limit and eradicate the infection is contraindicated.

CHEMOTHERAPEUTIC AND ANTIBIOTIC AGENTS. *Sulfonamides.* Parasulfonamide benzene-azo compounds and their derivatives were proved to have bactericidal qualities in 1919 by Heidelberger and Jacobs of the Rockefeller Institute. In 1935 Domagk[18] in Germany showed that this azo-dye had a selective curative action in streptococcic infections of mice. Colebrook and Kenny[13] in London (1936) showed excellent results with prontosil in the treatment of puerperal hemolytic streptococcic infection. Further chemical research resulted in the development of sulfanilamide and its derivatives. Their therapeutic value has been established in the treatment of infections caused by the hemolytic streptococcus, staphylococcus, pneumococcus, gonococcus, and *Clostridium welchii*. Their value seems to be questionable in the treatment of anaërobic streptococcal infections.

According to Gibberd,[24] the reduction in mortality of sulfonamide treated hemolytic streptococcus infections was associated mainly with a decrease in the widespread invasion of the tissues by the hemolytic streptococcus, rather than with a greater tendency to resolution of the disease, once widespread invasion had occurred. Foulis and Barr[22] obtained a mortality rate of 1.4% in their series of patients with puerperal sepsis treated with the sulfonamides. This they compared with a mortality rate of 13.4% in the preceding 5 year period when no chemotherapy was used. Sulfonamides

were given prophylactically to 493 puerperal women by Delmas and deKerleau[19] with a slight decrease in mortality and a considerable reduction in morbidity. Many other investigators[28,44,55] have used the sulfonamides in puerperal infections.

The sulfonamides most widely used at the present time are sulfadiazine, sulfathiazole and sulfamerazine. The complications of the sulfonamides include agranulocytosis,[23] acute hemolytic anemia, toxic dermatoses, urinary complications, and others less frequently seen.[47,61] Maintenance of the urinary output is the cardinal principle involved in prevention of urinary complications.

Penicillin. Penicillin is effective against the organisms usually found in cervical cultures, and should prove to be the drug *par excellence* in the prevention and treatment of puerperal infections.

In general, the gram-positive organisms are sensitive to penicillin, as also are the gram-negative cocci. The gram-negative bacilli are relatively insensitive. However, many of the gram-negative bacilli formerly considered totally insusceptible to penicillin are now known to be sensitive in various degrees, although far less so than the gram-positive bacilli.[31,65,71] Infections due to gram-negative organisms of any kind should not necessarily be considered outside the scope of penicillin therapy. Case reports are now appearing in which penicillin therapy has been successful in curing infections due to organism hitherto classed as resistant to penicillin.[33,40]

To date, most of the work concerning the use of penicillin in obstetrics has been to prove its transmission across the placenta to the fetal circulation and amniotic fluid.[27,32,38,80] Its prophylactic use in patients with prolonged labor and in those with premature rupture of the membrane has been suggested.

Synergism of penicillin with sulfonamides has not been established. Kirby[39] regards the action as additive rather than synergistic. The War Department Technical *Bulletin*[72] for March 1945 states that there is no clinical evidence of synergism between the 2 agents, and that the supplementary use of sulfonamides only contributes to the risk of untoward reactions and complications. Hobby and Dawson[35] have observed that sulfonamide *in vitro* increases the bacteriostatic action of penicillin only if the organism is sulfonamide-sensitive and present in small numbers. Douglas and Davis[20] believe that in mixed puerperal infections, where gram-positive cocci and gram-negative bacilli are present, both penicillin and sulfadiazine should be employed. Conclusions as to the benefit of combining the 2 drugs must await adequate chemical and clinical evidence.

The daily dose of penicillin varies with the type and severity of the infection. The tendency seems to be to use much larger doses of the drug if the usual daily doses of 100,000 to 200,000 units do not result in a clinical response. In severe infections the drug should be continued for several days after the temperature and pulse have become normal.

Streptomycin. Streptomycin, an antibiotic substance obtained from the mold *Actinomyces griseus*, supplements penicillin by arresting the growth of many of the gram-negative bacilli. It is freely distributed in the fetal circulation and amniotic fluid following intravenous administration to the mother at term.[79] At this time, insufficient clinical studies have been reported in its use in puerperal infections, but there is reason to believe it will prove itself a valuable addition to our present armamentarium.

Among the causes of maternal mortality, sepsis has dropped from first place, which it long held, to third.[57] This improvement is due to better obstetrical practice in general, and to the chemotherapeutic and antibiotic drugs.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF APRIL 16, 1946

Studies on Nutrition. The Effect of Preoperative Force Feeding on Surgical Patients. C. E. KOOP, M.D., J. DREW, M.D., C. RIEGEL, PH.D., and J. E. RHOADS, M.D. (Dept. of Surgery and Harrison Dept. of Surg. Research, Univ. of Penna.). A group of 24 patients undergoing major abdominal or intracranial operations have been studied for the effect of preoperative force feeding on the postoperative course. Of these patients, 12 were "force fed" approximately 0.9 gm. of nitrogen per kg. per day (about 3 times the average postoperative requirement) for 5 preoperative days. The remaining 12 patients served as controls.

Among the nutritional studies carried out before and after operation were nitrogen balance determinations, serum protein concentrations, and total circulating proteins.

Circulatory studies included blood and plasma volume determinations, the response of the patient's pulse, blood pressure and the state of consciousness to changes in position from the horizontal to the vertical on a tilt table, and ballistocardiographic tracings. These determinations were made at intervals before and after operation.

It was found that patients undergoing gastrectomy, colon resection and craniotomy could accumulate a nitrogen store well in excess of the deficit usually observed on inadequate intake after operation if they were force fed for 5 days preoperatively. This accumulation varied from 81 to 257 gm. of nitrogen for the 5 days.

Objective evidence obtained with the ballistocardiograph and the tilt table supported the clinical impression that the postoperative course is improved providing there is a sufficient preoperative accumulation of nitrogen to compensate for the deficit in the immediate postoperative period.

Relation of Nitrogen Balance and Blood Volume to Abnormalities of the Circulation in Convalescent Surgical Patients. R. L. MAYOCK, M.D., C. E. KOOP, M.D., C. RIEGEL, PH.D., N. T. KOUGH and ISAAC STARR, M.D. (Dept. of Therap. Research and the Harrison Dept. of Surg. Research, Hosp. of the Univ. of Penna.). The ballistocardiogram has been used in a search for abnormalities of convalescence following surgical operations. On 67 patients, 362 ballistocardiograms were made; in many of them nitrogen balance studies had been made. Abnormal ballistocardiograms were found more frequently in the patients whose nitrogen balance after operation became negative than in those whose balance was maintained by special feeding methods. This difference was statistically significant.

Cardiac output as calculated from the ballistocardiogram was compared with the result of estimations of blood volume made by the blue dye T-1824. There was significant positive correlation between cardiac output and blood volume, but the relationship was not a close one and changes in single individuals were sometimes the reverse of this relationship.

These results and other clinical criteria support the conclusion that the patients kept in nitrogen equilibrium by special feeding methods were actually in better physical condition than those allowed to go into negative nitrogen balance.

Electroencephalographic Evaluation of the Effect of Penicillin in Treatment of Central Nervous System Syphilis.* DONALD SCOTT, JR., PH.D., and GEORGE D. GAMMON, M.D. (Johnson Foundation for Med. Physics and Dept. of Neurology, Univ. of Penna.). Previous workers have reported the presence of significant abnormalities in the electroencephalographic record from cases of central nervous system syphilis. The present study of 30 cases found abnormal records in 60%, but the main interest was in developing the electroencephalogram as a method of evaluating the effect of penicillin treatment.

The patients were divided into 4 groups on a clinical basis (juvenile paresis, 3 cases; meningovascular syphilis, 8 cases; taboparesis, 9 cases; paresis, 10 cases). The electroencephalographic records were classed as either normal, questionable, or abnormal. The greatest percentage of abnormal records was seen among the paretic cases (70%), whereas the lowest incidence was seen in taboparesis (11%). In all cases where the pretreatment record was taken to be abnormal, a reduction in this type of activity was found when the patient was restudied after treatment. It was more difficult, however, to determine such changes in records which were originally considered questionable and no clear-cut shift could be seen in this group after treatment. In general, there was a rough correlation between the reduction in abnormality in the electroencephalogram and the clinical improvement in the patient. However, in most cases there was a residuum of minor abnormality after treatment, which agreed with the fact that in most cases the patient had not entirely recovered at the time the last electroencephalogram was made.

Of great interest was the prominence of the moderately slow (5 to 8 per second) waves in pretreatment records. These were present in 72% of the abnormal and questionable records. It was also found that in 56% of these records the alpha rhythm had a frequency below normal limits. It was hard to distinguish between these 2 situations, but where the frequency returned to the normal alpha range after treatment it was considered that the moderately slow waves were essentially an alpha pattern which had been slowed by the disease process. Whatever the correct identification of this activity the most noticeable change during treatment was the gradual disappearance or speeding up of the waves with frequencies between 5 to 8 per second.

* This work was done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the University of Pennsylvania. The University of Pennsylvania penicillin group includes Dr. John H. Stokes, responsible investigator, and Drs. Beerman, Ingram, Steiger, Gyorgy, Rose and Steele.

Effect of Globin From Human Erythrocytes on Plasma Volume and Diuresis.* MAX M. STRUMIA, M.D. (Bryn Mawr Hosp. and Graduate School of Medicine, Univ. of Penna.). The administration of a 4% solution of modified human globin made isotonic with sodium chloride or dextrose produces a rapid increase in blood volume closely equivalent to the amount given, as determined by plasma volume studies with the dye method. This increased plasma volume in the normal subject usually disappears at the end of 24 hours. Less than 5% of globin is lost in the urine and the bulk of the material appears to be utilized.

In the management of the nephrotic state of chronic and subacute glomerulonephritis, edema offers a challenge to the attending physician. A salt-poor diet, moderate and carefully controlled water reduction, a protein intake sufficient not only to maintain a positive balance but also to restore progressively lost protein reserve, proper cardiac stimulation if signs

* This work has been initiated with the aid of the Plasma Research Fund of the Bryn Mawr Hospital, and continued under contract recommended by the Committee on Medical Research of the Office of Scientific Research and Development.

of insufficiency exist, these are the basic elements of therapy. They are not, however always sufficient.

It is often necessary to reduce or eliminate edema by means of diuretics. As diuretic agents, urea, potassium chloride, ammonium chloride, mercopurin, plasma, human serum albumin, globin have been used with varying degrees of success.

In a series of carefully controlled experiments, globin has produced in patients suffering from chronic glomerulonephritis in the nephrotic state a prompt and abundant diuresis, with rapid disappearance of visible edema. During the period of observation, no restrictions were placed on the salt and water intake. Globin has proven effective as a diuretic whether the patient was in a positive nitrogen balance or not. Similar results have been obtained on hypoproteinemic edemas. In the cases so far studied, globin was employed as a 4% solution in 0.85% sodium chloride. Even better effect can be expected when globin is made isotonic with dextrose. Kidney functional studies done before and after administration of large doses of globin to nephrotic patients have shown no change. Two cases were presented in detail.

BOOK REVIEWS AND NOTICES

VITAMINS AND HORMONES. Advances in Research and Applications. Vol. III. Edited by ROBERT S. HARRIS and KENNETH V. THIAMIN. Pp. 452. New York: Academic Press, Inc. Price, $6.50.

THE 3rd volume of "Vitamins and Hormones covers 9 subjects as follows: The Interrelation of Vitamins, by Thomas Moore; The Synthesis of B Vitamins by Intestinal Bacteria, by Victor A. Najjar and Rachel Barrett; Sulfonamides and Vitamin Deficiencies, by Floyd S. Daft and W. H. Sebrell; Manifestations of Prenatal Nutritional Deficiency, by Josef Warkany; Growth Factors in Microbiology—Some Wider Aspects of Nutritional Studies With Microörganisms, by B. C. J. G. Knight; Possibilities in the Realm of Synthetic Estrogens, by E. C. Dodds; Chemistry of Anti-pernicious Anemia Substances of Liver, by Y. Subbarow, A. Baird Hastings, and Milton Elkin; The Mechanism of Action and Metabolism of Gonadotropic Hormones in the Organism, by Bernhard Zondek and Felix Sulman; The Rôle of Acetylcholine in the Metabolism of Nerve Activity, by David Nachmansohn.

This volume follows the same general plan of the first two and on the whole the articles are as well written; however, a few comments may be in order. There is some repetition in the second and third articles that probably could have been eliminated. In the article on prenatal nutritional deficiency, one is surprised to find so little regarding the effect of vitamin E. The review on growth factors in microbiology is more a monograph in itself than a chapter of a book. It takes up over 100 pages and covers the literature of this rapidly developing field in a masterly fashion.

The article on synthetic estrogens is largely a review of the author's own work and suggestions for future work. The author of the last article presents a good case for the acetylcholine theory of nerve conductance.

The difficulty of preparing such a volume and getting it into the hands of the reader in a fairly short time is emphasized by the fact that mention of pyridoxal, pyridoxamine, desthiobiotin, etc., and their activities in bacterial metabolism, was made only in notes added in proof. There are a few typographical errors such as on page 241 where Fitz-Hugh has become Fritz Hugh.

J. J.

PRINCIPLES OF DYNAMIC PSYCHIATRY. By JULES H. MASSERMAN, M.D., Division of Psychiatry, Dept. of Medicine, Univ. of Chicago. Pp. 322; 4 plates. Philadelphia: Saunders, 1946. Price, $4.00.

THE expressed purpose is to record here certain fundamentals of modern dynamic psychiatry, as yet only taught through lecture and precept. Another volume is to follow, entitled "Practice of Dynamic Psychiatry." In this book, Part I gives the scope of psychiatry, together with a critical consideration of behavioristic theories. Part II attempts to "reformulate and integrate these theories into a biodynamic organon of behavior."

Among the many topics discussed are: Psychiatry, the Science of Behavior; Psychologic Concepts of Behavior; Psychoanalytic Concepts of Behavior; The Dynamics of Adaptation; Neurotigenic Dynanisms; Psychotic Dynamisms; Biodynamic Correlates of Current Theories of Behavior; Development of a General Biodynamic Theory of Behavior; Biodynamic Formulations of Behavior; The Principle of Substitution; Principle of Conflict; Intensity of Conflict and Modes of Therapy; Biodynamic Processes of Language and of "Verbal" Therapy; A Critique of the Biodynamic Theory of Behavior. Most space is accorded Schizophrenic Mechanisms, discussed as Withdrawal from "External Contacts," and Blunting and Distortion of Affect, Thinking Disturbances in Schizophrenia, and Disturbances in Motor Patterns.

Throughout, the approach is definitely psychoanalytic, with the usual colorful wording, thereby rendering its exceptionally informative Glossary desirable. N. Y.

CLINICAL ROENTGENOLOGY OF THE HEART. Edited by JOHN B. SCHWEDEL, M.D. Pp. 380; 749 illus. New York, Hoeber, 1946. Price, $12.00.

THIS book is unquestionably one of the easiest to read concerning roentgenology of the heart that has yet been published. While this is partially due to the author's literary style, of more importance is the manner in which he has organized his material.

The book is divided into 14 chapters: The first 2 deal with technique and cardiac measurements; Chapters 3 and 4 concern the normal heart and its normal variations; Chapters 5, 6, 7 and 8 are particularly noteworthy as each chapter is devoted to one chamber of the heart. These should prove of considerable assistance to the student and certainly helps crystallize the thoughts of the trained radiologist. The author treats the aorta, venæ cavæ and the brachiocephalic vessels in the same way. The chapter on "Lungs and Heart Disease" deserves special comment. Its illustrations and microphotographs of lung sections are particularly instructive.

The pericardium, congenital heart disease, displacements of the heart, and cardiac and extracardiac calcifications are also treated in individual comprehensive chapters.

The publishers have done an excellent job. The paper used is of fine quality and the printing is large enough to read with ease.

Each roentgenogram is accompanied by an explanatory line-drawing; these are particularly valuable as they clearly illustrate the significant anatomic findings. The legends are uniformly clear and add considerably to the text. Unfortunately, the film reproductions are all positive prints, but their excellence compensates in large measure for this deficiency. P. H.

ADVANCES IN CARBOHYDRATE CHEMISTRY. Vol. I. By W. W. PIGMAN, B.S., A.M., PH.D., Corn Products Refining Co., Argo, Ill.; and M. L. WOLFROM, A.B., M.S., PH.D., Ohio State Univ., Columbis, O. Pp. 374. New York: Academy Press, 1945. Price, $6.00.

THIS book represents the first of a projected series of annual volumes to review important advances in the chemistry of carbohydrates including the sugars, polysaccharides and glycosides. Thirteen contributors join in the presentation of the 11 following reviews: The Fischer Cyanchydrin Synthesis and the Configurations of Higher-carbon Sugars and Alcohols (C. S. Hudson), 36 pages; The Altrose Group of Substances (N. K. Richtmyer), 40 pages; Carbohydrate Orthoesters (Eugene Pacsu), 51 pages; Thio- and Seleno-Sugars (A. L. Raymond), 17 pages; The Carbohydrate Components of the Cardiac Glycosides (R. C. Elderfield), 27 pages; Metabolism of the Sugar Alcohols and Their Derivatives (C. J. Carr and J. C. Krantz, Jr.), 18 pages; The Chemistry of the Nucleic Acids (R. S. Tipson), 53 pages; The Fractionation of Starch (T. J. Schoch), 32 pages; Preparation and Properties of Starch Esters (R. L. Whistler), 31 pages; Cellulose Esters of Organic Acids (C. R. Fordyce), 19 pages; A Discussion of Methods of Value in Research on Plant Polyuronides (Ernest Anderson and Lila Sands), 16 pages.

The authors have presented critical reviews of their respective subjects. Most of the reviews are of analytical and industrial interest though the contribution by Elderfield, Carr and Krantz, and Tipson are of definite biochemical interest. Adequate literature references are presented.

H. V.

HIDDEN HUNGER. By ICIE G. MACY, PH.D., Research Laboratory, Children's Fund of Michigan; and HAROLD H. WILLIAMS, B.S., PH.D., Research Laboratory, Children's Fund of Michigan. Pp. 286. Lancaster, Pa.: Cattel Press, 1945. Price, $3.00.

"HIDDEN HUNGER, Tragedy of the Unbalanced Diet" is a skillfully written record of the achievements and failures in applied nutrition. It provides an up-to-date and scientifically accurate story of the development of the field of nutrition. It places a major emphasis upon the improvement of human welfare through better nourishment, and in this respect is a natural outgrowth of the senior author's active rôle in research and in national conferences on health and nutrition.

A strong indictment is leveled against the nation for its failure to apply the recommendations of the White House Conference on Child Health and Protection (1930). If they had been adopted, perhaps the large

rejection rate of Selective Service candidates upon physical grounds would have been much reduced.

The nutrition of the infant, the child, the adult and the aged is discussed. Interesting comparisons are made of the Army rations and feeding practices in World Wars I and II. Much instructive information is given upon the experiences in improving the meals of factory workers during the war.

Relevant data and quotations are presented from many reports that are not readily available to the lay reader. There is an extensive bibliography, which is well indexed. It should appeal to readers in many fields of endeavor. H. V.

ADVANCES IN PROTEIN CHEMISTRY. Vol. II. By M. L. ANSON, Continental Foods, Hoboken, N. J.; and JOHN T. EDSALL, A.B., M.D., Harvard Med. School, Boston, Mass. Pp. 443. New York: Academic Press, 1945. Price, $6.50.

THIS is the second annual volume of a series concerned with recent advances in protein chemistry. Eleven chapters are devoted to reviews in the following fields: Analytical Chemistry of the Proteins (A. J. P. Martin and R. L. M. Synge), 63 pages; The Microbiological Assay of Amino Acids (E. E. Snell), 31 pages; The Amino Acid Composition of Food Proteins (R. J. Block), 13 pages; The Relationship of Protein Metabolism to Antibody Production and Resistance to Infection (P. R. Cannon), 18 pages; Terminal Amino Acids in Peptides and Proteins (S. W. Fox), 21 pages; The Copper Proteins (C. R. Dawson and M. F. Mallette), 62 pages; Mucoids and Glycoproteins (Karl Meyer), 23 pages; The Reactions of Formaldehyde with Amino Acids and Proteins (Dexter French and J. T. Edsall), 56 pages; Wheat Gluten (M. J. Blish), 21 pages; Protein Denaturation and the Properties of Protein Groups (M. L. Anson), 24 pages; *X*-Ray Diffraction and Protein Structure (I. Fankuchen), 17 pages.

Martin and Synge give the most extensive review of analytical methods available, documenting their discussion with well over 800 references. The review of microbiologic assay methods by Snell summarizes the available data in this rapidly developing field. Meyer's review of mucoids and glycoproteins is the first to appear in this field since Levene's monograph in 1925.

Many factual data appear as tables or charts in each chapter. Bibliographies are extensive and up-to-date. Few errors in proofreading are apparent. This volume can be recommended highly to all interested in proteins and amino acids. H. V.

THE FALLING SICKNESS. By OWSEI TEMKIN, M.D. Pp. 380. Baltimore: Johns Hopkins Press, 1945. Price, $4.00.

THE nature of epilepsy being still obscure and the border-line between the epilepsies and other nervous diseases indistinct, the author recognizes that its history cannot be written in the same sense that one might construct a history of tuberculosis, for instance. He has, therefore, called his book by the ancient name "The Falling Sickness," and has aimed at finding out what he could about "what was meant by epilepsy, what symptoms were attributed to it, how it was explained, and how treated" through its long past. Beginning with the ancient Greeks, the author has chosen to close with the period about 1880, "when the impact of Jackson's and Charcot's work made itself felt." This last item has required some 30 odd pages that are more in the domain of the neurologist than of the historian; however, it is handled with such a sure touch that one regrets that the same skill was not applied to the rich history of epilepsy in the past 60 years as well. To be sure, the more recent the events, and the greater their number, the more difficult is the historian's task; but we can be confident that the result would have been far more than a mere catalogue of names and—just as in the case of the Charcot-Jackson discussion—would have helped further to understand the present status of the subject. When the author has so well completed his self-appointed task, one should not, perhaps, cry for more. Yet one cannot help but wish that the story had been made more complete by the inclusion also of a consideration of epilepsy among the primitives and in Far Eastern civilizations. We know of no full history of the subject in English in spite of all that has been written about it.

An adequate detailed critical review of this scholarly monograph could scarce be done except by another professional histor-

ian of medicine. Nor could such a review be reproduced in, or suitable for, a journal such as this one. However, we can guarantee that a careful perusal of this excellent study will provide the reader with much more medical history than that included in the history "The Falling Sickness."

E. K.

EXERCISES IN HUMAN PHYSIOLOGY. By SIR THOMAS LEWIS, University College, London. Pp. 103; 8 illus. London: MacMillan, 1945. Price, $1.25.

THIS small book lives up to the reputation of its author. It describes a number of relatively simple fundamental experiments that Sir Thomas himself developed. He has selected those most readily applicable to the teaching of medical students, omitting the more elaborate and painful experiments for which he is so justly renowned. Many of the experiments described are commonly utilized for teaching, such as venous pressure estimates (direct and indirect methods), indirect arterial pressure measurements, arterial and venous pulse curves, electrocardiograms, and histamine reactions. Others less commonly considered are local anesthetization of the ulnar nerve, vasomotor reactions to temperature, reactive hyperemia, inflammatory hyperesthesia, etc. All the experiments described are useful and the book should be of great value to teachers. Even in the familiar experiments, the descriptions are given a new value by the inclusion of Sir Thomas' own clinical viewpoint and by his insistence on the necessity of careful observation.

The only criticism that might be raised is that the exercises are for the most part qualitative. The newer elaborate mechanical devices that make qualitative studies now more accurate and complete are not considered. For this reason the work is perhaps the better for the training of medical practitioners and the worse for the development of physiologists and clinical research workers.

H. B.

BIOLOGICAL ACTIONS OF SEX HORMONES. By HAROLD BURROWS. Pp. 514. Cambridge University Press, 1945. Price, $8.50.

THE purpose of this book is to coördinate and summarize experimental findings in the field of the sex hormones. It is confined largely to biologic work done in the laboratory rather than the clinic.

The Reviewer, who has put this book to the test of determining how usable it is, has found that, in the search for the experimental evidence that has established various facts, data could be readily found in considerable detail which otherwise would have necessitated laborious search through the literature. This means that the index is sufficiently detailed in cross-references and that the discussion of the literature has been well organized in the substance of the book. It can be highly recommended as a work for reference.

I. Z.

NEW BOOKS

Current Therapies of Personality Disorders. By BERNARD GLUECK, M.D., President, The American Psychopathological Association. Pp. 296. New York, Grune & Stratton, 1946. Price, $3.50.

Treatment by Ion Transfer (Iontophoresis). By D. ABRAMOWITSCH, M.D., Physician-in-Charge of the Physiotherapy Dept., Lincoln Hosp., New York City; and B. NEOUSSIKINE, M.D., Tel-Avio. Pp. 192; Bibliography and Index. New York: Grune & Stratton, 1946. Price, $4.50.

Cosmetics and Dermatitis. By LOUIS SCHWARTZ, M.D., Medical Director, U. S. P. H. S.; Chief, Dermatoses Sect., Div. of Industrial Hygiene; Adj. Professor in Dermatology, Georgetown Univ. School of Medicine; Assoc. Clin. Professor in Dermatology and Syphilology, New York Univ. Coll. of Medicine; Consultant, Office of Price Administration; and SAMUEL M. PECK, M.D., Medical Director (R), U. S. P. H. S.; Assoc. Attend. Dermatologist, Mt. Sinai Hosp., New York City; Attend. Dermatologist and Syphilologist, Skin and Cancer Unit of the New York Post-Graduate Medical School and Hosp. of Columbia Univ.; Diplomate of the American Board of Dermatology and Syphilology. Pp. 198; 20 illus. New York: Hoeber, 1946. Price, $4.00.

Doctors East, Doctors West. By EDWARD H. HUME, M.D. Pp. 278; 21 illus. New York: Horton, 1946. No price given.

An American physician's life in China.

Diseases of the Adrenals. By LOUIS J. SOFFER, M.D., Adj. Attend. Physician, The Mount Sinai Hosp., New York City. Pp. 304; 44 illus. Philadelphia, Lea & Febiger, 1946. Price, $5.50.

The Herbal of Rufinus. By LYNN THORNDIKE (Editor, from the Unique Manuscript). With the assistance of FRANCIS S. BENJAMIN, JR. Pp. 467. Chicago: Univ. of Chicago Press, 1945. Price, $5.00.

Corky the Killer. A Story of Syphilis. By HARRY A. WILMER, B.S., M.S., M.B., M.D., PH.D. in Pathology. With an Introduction by PAUL A. O'LEARY, M.D., Head, Section on Dermatology and Syphilology, Mayo Clinic; Professor of Dermatology and Syphilology, Mayo Foundation, Univ. of Minnesota. Pp. 67; 33 illus. New York: American Social Hygiene Assn., 1946. Price, $1.00.

This book is prepared for the lay public. It has a triple form of presentation, and is a combination of phantasy and fact to help remove public fears and misunderstandings relating to syphilis.

The Traumatic Deformities and Disabilities of the Upper Extremity. By ARTHUR STEINDLER, M.D., F.A.C.S., Professor and Head of the Dept. of Orthopedic Surgery, The State Univ. of Iowa; in collaboration with JOHN LOUIS MARXER, M.D., Assoc. Orthopedic Dept., the State Univ. of Iowa. Pp. 515; 1048 illus. Springfield, Ill.: Thomas, 1946. Price, $10.00.

Physiotherapy. By THOMAS F. HENNESSEY, M.D., Dean and Director, Massachusetts School of Physiotherapy, Boston. Pp. 20. Indiana: Bellman, 1946. Price, $.75.

The Venous Pulse and Its Graphic Recording. By FRANZ M. GROEDEL, M.D., Attend. Cardiologist, Beth David Hosp.; Cardiologist, St. Anthony's Hosp., New York City; Consult. Cardiologist, Einhorn Dept. of Lenox Hill Hosp., New York City. Pp. 223; 114 illus. Brooklyn, N. Y.: Medical Press, 1946. Price, $5.50.

La Electroforesis de Sulfonamidas para el Tratamienio de los Procesos Infecciosoinflamatorios Localizados. By CAMILO SCHMEHLIK, DR. MED., Univ. le la Universidad de Viena f Licenciado de la Universidad de Madrid. Pp. 92. Madrid, Spain: Editorial Gran Capitan, 1945. No price given.

In this booklet the original text is given in Spanish, English, German and French

Unhappy Marriage and Divorce. By EDMUND BERGLER, M.D. With an Introduction by A. A. BRILL, M.D. Pp. 167. New York: International Univ. Press, 1946. Price, $2.50.

A study of neurotic choice in marriage partners.

Motor Disorders in Nervous Diseases. By ERNST HERZ, M.D., Instructor in Neurology, Coll. of Physicians and Surgeons, Columbia Univ.; and TRACY J. PUTNAM, M.D., Professor of Neurology and Neurologic Surgery, Coll. of Physicians and Surgeons, Columbia Univ. Pp. 184; 250 illus. New York: King's Crown Press, 1946. Price, $3.00.

The Medical Clinics of North America. Postwar Medicine. Pp. 485; 76 illus. Philadelphia: Saunders, 1946. Price, $16.00 yearly.

Tratado de Cardioangiologia. By PEDRO A. TAPELLA, Docente Libre de Patologia Medica en la Facultad de Buenos Aires. Pp. 946. Buenos Aires: Lopez & Etchogoyen S.R.L., 1946. No price given.

Tratado de Patologia Medica por el DR. RODOLFO DASSEN, Laureado por la FAC. de Medicina de BS. AS (Medalla de Oro), Ex Docente Libre de Clinica Medica (BS. AS.), Medico del Hospital de Clinicas, Sala IV (BS. AS.). Pp. 827. Buenos Aires: Lopez & Etchegoyen S.R.L., 1946. No price given.

In English this "Medical Pathology" would probably be called a Text Book of Medicine, as it includes, in each of the diseases considered, a clinical description, diagnosis, prognosis and treatment as well as the different aspects of Pathology. Volume I covers Infectious Diseases, Diseases of the Cardiovascular System, the Blood and the Urinary Tract, also of the Spleen and Lymph Nodes. It contains a brief Index but no references.

Valor Pronostico del Electrocardiograma por el DR. MANUEL VELA. III. Ponencia. Pp. 336. Madrid: Libreria Editorial Cientifico Medica Espanola, 1946. No price given.

Publicaciones del Centro de Investigaciones Tisologicas. By ROQUE A. IZZO, Professor. Pp. 280. Buenos Aires, Pabellon "Les Provincias," 1945. No price given.

Spezielle chirurgische Therapie für Studierende und Arzte. Vol. 2. By DR. MAX SAEGESSER, Privatdozent für Chirurgie, Bern. Pp. 884. Bern: Medizinischer Verlag Hans Huber, 1946. Price, $20.00.

Valor Pronostico del Electrocardiograma Appendice de Quadros Estadisticos por el DR. MANUEL VELA. III. Ponencia. Pp. 336. Madrid: Libreria Editorial Cientifico Medica Espanola, 1946. No price given.

It's How You Take It. By G. COLKET CANER, M.D., Associate in Neurology, Massachusetts General Hosp.; Psychiatrist in Dept. of Hygiene, Harvard Univ. Pp. 152. New York: Coward-McCann, 1946. Price, $2.00.

The purpose of this book is to bring together common sense and useful information which every person over 16 should have about the use of the mind and effect of emotion, and about types of reactions to the opportunities and difficulties that everyone meets.

Journal of Colloid Science. Vol. I, No. 1 (bi-monthly). Editor-in-Chief, VICTOR K LAMER, Columbia Univ., New York. New York: Academic Press, 1946. Price, $10.00 yearly.

We welcome this new Journal in a special field closely allied to medicine and are confident that it will produce much valuable information and stimulation on matters that are of basic importance to all branches of biology. The high standing of its editors and consulting committee is a good guarantee that the undertaking will be well carried out.—E. K.

Asma Alergia por el DR. GUIDO RUIZ MORENO, Jefe de la Seccion Alergia del Instituto de Investigaciones Fisicas aplicados a la Patologia Humana, de la Academia Nacional de Medicine; Jefe del Consulterio de Algeria del Hospital Britanico de Buenos Aires; Miembro Titular de la Sociedad Argentina de Alergia; Membro Honorario del "American College of Allergists;" Miembro correspondiente de la "American Association for the Study of Allergy;" Miembro de "The International Correspondence Club of Allergy;" Docente Libre de Higiene y Medicina Social de la Facultad de Ciencias de Buenos Aires. Pp. 186. Buenos Aires: Lopez & Etchegoyen S.R.L., 1946. No price given.

Digitalis and Other Cardiotonic Drugs. By ELI ROBIN MOVITT, M.D., Capt., M.C., A.U.S.; Diplomate of American Board of Internal Medicine; Internist, Veterans Administration Facility, San Francisco, Calif. Pp. 203. New York: Oxford Univ. Press, 1946.

Enfermedades de los Pies. Vol. 40. Coleccion Espanola de Monografias Medicas, Director: DR. J. PUIG SUREDA. Pp. 128. No price given.

Essentials of Clinical Proctology. By MANUEL G. SPIESMAN, B.S., M.D., Proctologist, Mt. Sinai and Edgewater Hosps.; Consult. Proctologist, Grant, Henrotin and St. Elizabeth Hosps.; former Head of the Cook County Hosp. Rectal Clinic. With a Foreword by ANTHONY BASSLER, M.D., F.A.C.P., LL.D., Consult. Gastro-enterologist, St. Vincent's and other hospitals in New York City. Pp. 250; 62 illus. New York: Grune & Stratton, 1946. Price, $4.00.

Shock Treatments and Other Somatic Procedures in Psychiatry. By LOTHAR B. KALINOWSKY, M.D., Res. Associate in Psychiatry, Coll. of Physicians and Surgeons, Columbia Univ., and New York State Psychiatric Inst. and Hosp.; Assist. Neurologist, Neurological Inst. of New York; and PAUL H. HOCH, M.D., Assist. Clinical Psychiatrist, New York State Psychiatric Inst. and Hosp.; Instructor in Psychiatry, Coll. of Physicians and Surgeons, Columbia Univ. With a Foreword by NOLAN D. C. LEWIS, M.D., Professor of Psychiatry, Coll. Physicians and Surgeons, Columbia Univ.; Director of the New York State Psychiatric Inst. and Hosp. Pp. 320. New York: Grune & Stratton, 1946. Price, $4.50.

Scientific, Medical, and Technical Books Published in the United States of America, 1930–1944. Edited by R. R. HAWKINS, Chief of the Science and Technology Division, New York Public Library. Pp. 1114. New York: United States International Book Association, 1946. No price given.

NEW EDITIONS

Clinical Laboratory Diagnosis. By SAMUEL A. LEVINSON, M.S., M.D., PH.D., Director of Laboratories, Research and Educational Hosps., Chicago, Ill.; Professor of Pathology, Univ. of Illinois Coll. of Medicine; and ROBERT P. MACFATE, CH.E., M.S., PH.D., Assist. Director of Laboratories, Research and Educational Hosps., Chicago, Ill.; Asst. Professor of Pathology, Univ. of Illinois Coll. of Medicine. 3rd ed. Pp. 971; 207 illus. Philadelphia: Lea & Febiger, 1946. Price, $10.00.

An Outline of Organic Nitrogen Compounds. By EDWARD F. DEGERING, Dept. of Chemistry, Purdue Univ., and Collaborators. 4th ed. Pp. 752. Ypsilanti: Univ. Lithoprinters, 1945. Price, $7.50.

Rehabilitation, Its Principles and Practice. By JOHN EISELE DAVIS, M.D., Sc.D., Veterans Administration Facility, Perry Point, Md. 2nd ed. Pp. 264. New York: Barnes, 1946. Price, $3.00.

Starling's Principles of Human Physiology. By C. LOVATT EVANS, D.Sc., F.R.C.P., F.R.S., LL.D. (BIRM.), Jodrell Professor of Physiology in University College, London. 9th ed. Pp. 1155; 668 illus. Philadelphia: Lea & Febiger, 1945. Price, $10.00.

Essentials of General Anæsthesia. By R. R. MACINTOSH, M.A., M.D., F.R.C.S., D.A., Nuffield Professor of Anæsthetics, Univ. of Oxford; Consult. Anæsthetist to the Royal Air Force; Anæsthetist to the Radcliffe Infirmary, Oxford; late Anæsthetist and Lecturer in Anæsthetics, University Coll. Hosp. Dental School; Anæsthetist, Golden Square Ear, Nose and Throat Hosp.; Assist. Anæsthetist, Guy's Hosp. Dental School; and FREDA B. BANNISTER, M.A., M.D., D.A., First Assistant, Nuffield Dept. of Anæsthetics, Univ. of Oxford; Anæsthetist to the Oxford Eye Hosp.; late Clin. Assistant in Anæsthetics, University Coll. Hosp. Dent. School. 3rd ed., 2nd reprint. Pp. 341; 239 illus. Springfield, Ill.: Thomas, 1945. Price, $5.50.

CORRECTION

On page 480 (April number) in the heading of the Progress Department of Dermatology and Syphilology, the name of JOHN STOKES, M.D., was unfortunately omitted. The lines should read: "Under the charge of John Stokes, M.D., Herman Beerman, M.D., and Norman R. Ingraham, Jr., M.D., Emeritus Professor and Assistant Professors, respectively, . . ." On page 490, 18 lines from the bottom of the first column, "of the skin" should be followed by "is the epidermal."

NOTICE AND INSTRUCTIONS TO CONTRIBUTORS

MANUSCRIPTS intended for publication in THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMBHAAR, School of Medicine, University of Pennsylvania, Philadelphia 4, Pa. Articles are accepted for publication in THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively, except in the case of subsequent publication in Society proceedings.

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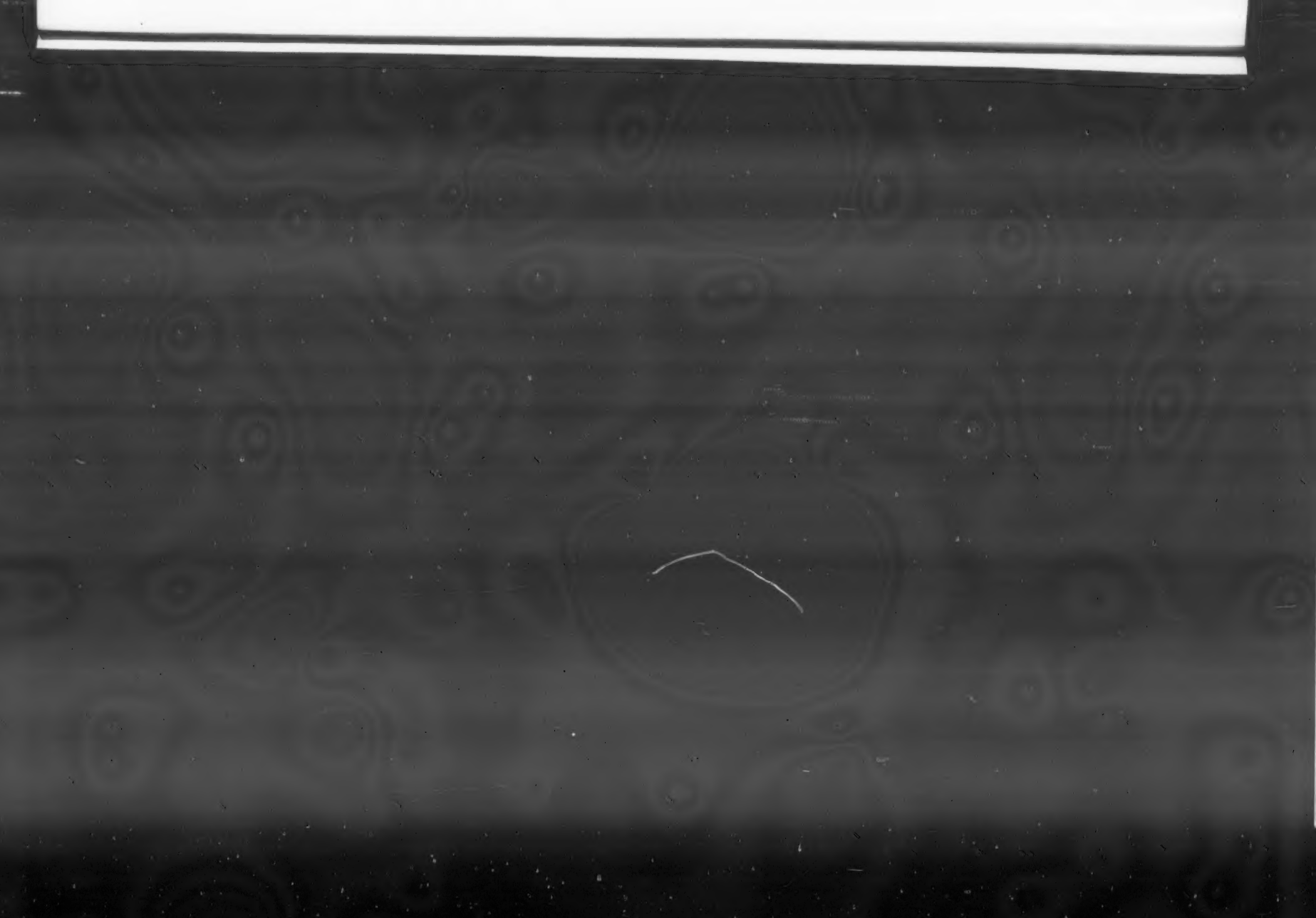

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